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Medical Ethics: The Jewish Point of View

Donald Gribetz, M.D., and Rabbi Moshe D. Tendler, Ph.D.,
Guest Editors

From The Page and William Black Post-Graduate School of Medicine

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CONTENTS

The Mount Sinai Journal: Past
Lester R. Tuchman, M.D. i

The Mount Sinai Journal: Future
David A. Dreiling, M.D. v

MEDICAL ETHICS: THE JEWISH POINT OF VIEW

Introduction *Donald Gribetz, M.D., and Rabbi Moshe D. Tendler, Ph.D.* 1

I. BEGINNING OF LIFE

In Vitro Fertilization and Extrauterine Pregnancy ("Test-Tube" Baby) *Ruth Freeman, M.D.* 3

Comment *Rabbi Moshe D. Tendler, Ph.D.* 7

Abortion on Demand *Joseph J. Rovinsky, M.D.* 12

Genetics, Amniocentesis, and Abortion *Kurt Hirschhorn, M.D.* 15

Teenage Pregnancies and Abortion *Joan E. Morgenthau, M.D.* 18

Comment *Rabbi David M. Feldman* 20

The Infant: Right to Privacy and Patient's Right to Know *Irwin Krasna, M.D.* 25

Comment *Rabbi Moshe D. Tendler, Ph.D.* 29

The Infant with Severe Anomalies: Should Life-Saving Surgery Be Performed? *Ira Greifer, M.D.* 32

Comment *Rabbi Leonard Kravitz* 34

Discussion *Moderator: Donald Gribetz, M.D. Discussants: Rabbi David M. Feldman, Rabbi Macy A. Gordon, Kurt Hirschhorn, M.D., Irwin Krasna, M.D., Rabbi Leonard Kravitz, Joseph J. Rovinsky, M.D., and Rabbi Moshe D. Tendler, Ph.D.* 37

continued

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Medical Center of Chicago

Mount Sinai
MEDICAL CENTER OF
GREATER MIAMI

II. ADOLESCENCE TO ADULTHOOD

The Rights of Adolescents in a Medical Setting *J. Gerald Young, M.D.* 42

Comment *Rabbi David M. Feldman* 49

Transplantation Surgery *Ira Greifer, M.D.* 52

Comment *Rabbi Moshe D. Tendler, Ph.D.* 54

Risk-Benefit Ratio: Hazardous Surgery and Experimental Therapy *Fred Rosner, M.D.* 58

Comment *Rabbi Moshe D. Tendler, Ph.D.* 60

Discussion *Moderator: Donald Gribetz, M.D. Discussants: Rabbi David M. Feldman, Ira Greifer, M.D., Fred Rosner, M.D., and Rabbi Moshe D. Tendler, M.D.* 65

III. END OF LIFE

Definition of Death and Dying *Bernard Kabakow, M.D.* 69

Comment *Rabbi David M. Feldman* 73

Autopsy *Stephen A. Geller, M.D.* 77

Comment *Rabbi David M. Feldman* 82

Old Age: Right to Privacy and Patient's Right to Know *Robert N. Butler, M.D.* 86

Comment *Rabbi Macy A. Gordon* 89

Discussion *Moderator: Donald Gribetz, M.D. Discussants: Robert N. Butler, M.D., Rabbi David M. Feldman, Stephen A. Geller, M.D., Rabbi Macy A. Gordon, Ira Greifer, M.D., Rabbi Moshe D. Tendler, Ph.D., and Rabbi Isaac Trainin* 92

IV. TRIAGE OF SCARCE RESOURCES

Triage: From Government to Institutions *Thomas C. Chalmers, M.D.* 101

Triage: From Institutions to Departments *Martin S. Begun* 104

Comment *Rabbi Moshe D. Tendler, Ph.D.* 106

Triage: From Departments to Patients *Ira Greifer, M.D.* 110

Comment *Rabbi Marc A. Gellman, Ph.D.* 113

Discussion *Moderator: Donald Gribetz, M.D. Discussants: Martin S. Begun, Thomas C. Chalmers, M.D., Rabbi Marc A. Gellman, Ph.D., Ira Greifer, M.D., and Rabbi Moshe D. Tendler, Ph.D.* 116

The Mount Sinai Journal: Past

The Mount Sinai Journal of Medicine, nee *The Journal of the Mount Sinai Hospital,* is now fifty years of age. Note I do not say "old"—under the direction of its present editor and editorial board it is young, vibrant, and growing. Fifty years is not a hoary age for a medical journal, but it is venerable, or at least respectable, and as one involved with the *Journal* from its beginning there is the risk of being either self-laudatory or self-deprecatory.

A rereading of early issues provides a picture of the state of the art as then practiced at The Mount Sinai Hospital and insights into the giants of those days, as well as their appreciation of the giants who preceded them. As an example, volume 1, number 1, dated May 1934, contains an obituary by Edwin Beer, himself a towering figure and a founder of modern urology, of Dr. Alexis Moschowitz.

As Beer tells it, Dr. Moschowitz "did much to elucidate the problems of surgery of the appendix, of hernia, of neoplasia of the heart, of emphysema . . . as well as numerous other diseases and conditions." He devised the modern surgical method of repair of femoral hernia.

Dr. Robert T. Frank, pioneer in the study of female hormonal levels in the blood and of the endocrinology of the ovary, wrote on tumors of the presocral retroperitoneal space. Dr. J. B. Collip, from the Department of Biochemistry at McGill, contributed the paper "Recent Advances in the Physiology of the Anterior Pituitary," including his very early work on the growth hormone and fascinating descriptions of antihormones.

Dr. Bela Schick, of the Schick test and—more importantly—with Pirquet the founder of modern immunology, appears for the first time in volume 2, with a description of a case of congenital malaria. In that volume also appear the clinical pathological conferences of Doctors Baehr and Klemperer, which each Wednesday packed the auditorium to the rafters in violation of the fire laws. Case reports of high quality are brief and significant.

In volume 4 Dr. Howard Lilienthal, Nestor of American surgery, describes (page 20) the first citrate transfusion ever given, in which he administered 700 cc of blood by the citrate method devised by Dr. Lewisohn. The date was January 26, 1915, the place the surgical ward of Mount Sinai Hospital. Other contributors to this volume were Dr. Albert A. Berg, virtuoso of the scalpel; Dr. B. B. Crohn, recently deceased at 100 years, then a rising young gastroenterologist; Dr. B. S. Oppenheimer; Dr. Samuel Geist; the then-rising John Garlock. Additionally there were Reuben Ottenberg, the blood-grouping pioneer, remarking on the history of blood transfusions. Dr. Paul Klemperer, giant in pathology, saint among men, great teacher, great investigator, appears for the first time in our pages. Dr. Percy Klingenstein and Dr. Len Ginzburg, both still vigorous and young of heart, are represented by fine papers.

In a brilliant short paper, a classic for its time, Masters Jaffe and Dack advocate depressing the basal metabolic rate to −20 by an 800-calorie diet as an alternative to total thyroidectomy, which extreme procedure had earlier been vigorously proposed by Blumgart, Levine, and Berliner in cases of acute coronary thrombosis.

Sir Henry Dale has a brilliant lecture, "Acetylcholine as a Chemical Transmitter of the Effects of Nerve Impulses," in the January 1938 issue (page 401). Volume 4 concludes with a festschrift in honor of Dr. Edwin Beer too massive and too important in its content to be summarized. I recommend its reading.

Volume 5 includes, inter alia, a festschrift to Dr. Israel Strauss, including contributions from Emanuel Libman, Charles Elsberg, George Hassin, Morris Bender, Edwin A. Weinstein, Walter B. Cannon (down from Harvard to deliver William H. Welch Lectures on Homeostasis and Homeostasis in Senescence), fascinating and ahead of his time.

Volume 7, number 1, dated May-June 1940, carries the first masthead, although the *Journal* had already lived through six busy, productive years. Dr. Joseph Globus was editor-in-chief, with Drs. Eli Moschowitz, Charles Friedberg, Samuel Klein, and Louis Soffer as assistant editors. However, Dr. Globus was the captain, the crew, and the bo'sun tight of our good ship Nancy Bell. It was his drive, his industry, his zeal, his good-hearted and never-misunderstood bluster which was the driving force of the *Journal*. Without Dr. Globus the *Journal* would never have survived.

Volume 7, number 5, honors Dr. Howard Lilienthal on his eightieth birthday. The tribute to him by Dr. Evarts Graham, master in his own right, is required reading. It is awesome to remember Dr. Lilienthal talk about pre-aseptic surgery that was not much different from surgery in the Middle Ages, and in terms that showed him alive to the future. He exhorted us to find out how the leech prevented blood clotting and to apply the lessons to surgery and medicine. In his person he was among the first to do cholecystectomy, and with Willy Meyer and Rudolph Matas composed the triumvirate responsible for the initiation of chest surgery in America. Dr. Lilienthal was among the first, if he was not the very first, to do successful lobotomy and lobectomy for bronchogenic carcinoma of the lung.

Volume 8, number 5 is a massive tome, some 800 pages, comprising a festschrift in honor of Dr. B. S. Oppenheimer. The one hundred fine papers concerning a broad spectrum of medicine and surgery should be required reading for those of us who think that everything we know today was discovered yesterday or last week. To pick several would be unfair to all the others.

The first mention of World War II in the *Journal* is a 1942 report on a conference on venereal disease control needs in wartime in volume 9 (page 207). The same volume includes a tribute to Dr. B. S. Sachs that is massive in size and extraordinary in quality, from the most eminent neurologists, neurosurgeons, and psychiatrists in America. A tribute to Dr. Hiram Vineberg in volume 10 contains two provocative short papers, one from Dr. Vineberg on his study of the relative immunity of Jewish women to carcinoma of the cervix, written in 1919, and the other a proposed treatment of coronary thrombosis with hirudin advocated by Dr. Howard Lilienthal.

By 1944, the Editorial Board had been expanding to include Ira Cohen, Leo Edelman, Joseph Harkavy, Eli Moschowitz, Albert Cornell, Solon Bernstein, Harold Neuhof, William Hitzig, I. S. Rubin, Samuel Silbert, Seymour Wimpfheimer, and Frederick Zeman. But the driving force remained Dr. Globus, always demanding, irascible at times, vocal but productive. With volume 13, May-June 1946, Lester Tuchman was added to the Editorial Board.

Volume 14 was fleshed out in quantity and quality by a superb tribute to Dr. I. C. Rubin, who is most remembered for insufflation of the fallopian tubes. Included are classics in this field. The ending of the era of the old surgical virtuosi was appropriately marked by the voluminous festschrift to honor Dr. A. A. Berg. Its contents are a gold mine. In another discipline, psychosomatic medicine, this volume has one of the finest short papers on emotional factors in internal disease I have ever read—by Dr. J. Gruen, recounting his transition from "scientific medicine" in the University of Amsterdam to his work as physician to fellow inmates in a concentration camp.

A bonus from the Holocaust, sad because of the reason for it, was the eightieth birthday celebration for Professor Ernest Pick, with contributions from the cream of displaced European scholars lucky enough to escape, and from his pupils, who were among the last of the young American physicians to go to Vienna for training at the Pick Institute for Pharmacology. The tribute of Dr. George Baehr must be read for its picture of the bygone era.

Dr. Joseph Globus died November 1952. He was succeeded by Dr. Solon Bernstein, who held the reins (or the blue pencil) briefly, dying untimely from brain tumor after bringing out one issue.

By wheedling and coaxing, Dr. Lester Tuchman, as editor, was responsible from volume 21 to 46. His initial editorial speaks for itself.

> Twenty years ago the late Joseph Globus wrote the opening editorial for the *Journal of the Mount Sinai Hospital,* setting it in the path it followed until his death two years ago. The brief tenure of Solon Bernstein, interrupted by his illness and terminated so abruptly by his untimely death, saw no change in these policies.
>
> It is now the duty of the new Editor and the Editorial Board to re-examine the purpose of the *Journal*, and either to reaffirm the old aims or fix new ones.
>
> We believe that a major aim of the *Journal*, now as then, is to make available its pages for case reports based upon the extraordinary clinical material which our Hospital has always had, some of which might otherwise be lost. Close observation, accurate, concise description, and detailed reporting are to be encouraged. We hope to foster the type of medical writings exemplified so brilliantly by men like Parkes Weber, and our own great Emanuel Libman. The *Journal* would prefer these papers to come from the ranks of the House and Resident Staffs, Fellows and younger men generally. We are therefore offering an annual prize to be known as the Joseph H. Globus Memorial Prize for the best such paper published in the *Journal* during each calendar year. The prize may not be won by anyone of Associate or Attending rank and is open to all other Mount Sinai Hospital workers. The subject may pertain to any clinical aspect of medicine, surgery, or the other specialties, based upon material from The Mount Sinai Hospital.
>
> At the other end of the spectrum we hope to publish from time to time fruits of the maturity, wisdom and experience of our Nestors, our Elder Statesmen, men who through their own medical lives and those of their teachers have encompassed all the rise of modern medicine—men who have themselves made and in most instances are continuing to make many of the contributions which have made our hospital great. From them we hope for philosophy, for perspective, for prophecy, for new directional signposts, for approbation and admonition.
>
> From the active workers of established position we desire no more than a tithe of their productivity.
>
> The clinico-pathological conferences and the monthly conferences are rich mines ripe for exploitation, the many named lectures will continue to be reported whenever possible. Brief general reviews of newer expanding experimental fields by men who are making their own contributions within them will be welcomed.

> Finally, we hope that the *Journal* will be representative of all the Hospital and every department, and that every worker, clinical or laboratory, will support it, read it, and write for it.

Material was difficult to come by at first, but that first volume offered an important article by Dr. Gregory Schwartzman, a highly original contribution by Dr. Henry Mirsky, a paper from a young recent resident named Eugene Braunwald, now a world-famous teacher at Harvard, as well as an exceedingly popular and sought-after review on pancreatitis by the present editor, Dr. David Dreiling, in collaboration with Alexander Richman. Clinico-pathological conferences had gone into decline nationwide, and in the *Journal* these reports were discontinued. Symposia on topical subjects were promoted, and a very popular department, Radiological Notes, was initiated by Dr. Bernard Wolf, chief of radiology, and afterward carried on by Dr. Claude Bloch with great dedication and ability. Some of the symposia brought out as monographs have become museum pieces.

With volume 23 in 1956 we went from the awkward May 1st to April 30th year to the calendar year, to everyone's satisfaction, and 1957 was a banner year. Volume 24 ran to 1,376 pages of exceptionally fine material, including a festschrift from pupils and friends to honor Dr. Paul Klemperer, possibly the best-loved man in the history of the Hospital and a pathologist without peer in the world. The rough years following the death of Dr. Globus were forgotten, no one murmured "bury the *Journal*" any more, tranquility reigned. Dr. Dreiling had come aboard in 1961 and was immediately an important asset. The hospital lost by death Dr. Klemperer, Dr. Eli Moskowitz, Harold Neuhof.

In 1965, the Department of Cardiovascular Surgery produced for the *Journal* an issue of exceedingly high quality in honor of Dr. Howard Lilienthal. Rivalling that issue in quality is number 3, on iron and iodine metabolism, from the Departments of Hematology, Physics, and Medicine and under the editorial aegis of Dr. Solomon Silver, a pioneer expert on the thyroid gland. In the *Journal* pages we meet computers ("Computer Learning and the Scientific Method") as early as 1965.

Clinico-pathological conferences had by then returned to the *Journal,* first under Dr. Fenton Schaffner, then in 1965 under Dr. F. Klion. In 1966 two issues require special mention, both from the Department of Neurology under its dynamic then chief, Dr. Morris Bender: "The Approach to Diagnosis in Modern Neurology, Part I: Clinical Bedside Examinations" (number 3), and "Part II: Laboratory Aids to Clinical Diagnosis" (number 4). Together they are gems. In 1966 American surgery and The Mount Sinai Hospital lost Dr. John Garlock.

The advent of the Mount Sinai School of Medicine was noted in 1967 and celebrated in the *Journal* by papers from its movers and shakers within our own walls—Dr. Hans Popper, Dr. George James, Dr. Irving Schwartz, Dr. Tibor Barka, Dr. M. Ralph Kaufman—and papers from a score of other renowned medical educators around the world.

The dedication on October 20, 1968 of the Mount Sinai School of Medicine of The City University of New York was hailed by addresses by four Nobel laureates reprinted in the *Journal* in volume 36. The authors were Dr. George Beadle ("On Medicine in a Changing World"), Dr. Francis H. C. Crick ("Molecular Biology and Medical Research"), Sir Peter Medawar ("Genetics and the Medicine of the Future"), and Dr. Linus Pauling ("Medicine in a Rational Society").

Recognition of the broader base on which the *Journal* now stood resulted in a change of name, from *Journal of the Mount Sinai Hospital* to *The Mount Sinai Journal of Medicine,* with number 3 in 1970. The editor and editorial staff now had a respite from the old hat-in-hand days, the end of wheedling and high-pressure salesmanship. A mark of the new era was the publication of two issues as a festschrift to Dr. Gutman—a true festschrift, because the contributors, distinguished investigators and teachers of medicine in their own right, were his former residents, now in important medical seats of their own in all parts of the United States. In its distinctive hyperbole the Talmud says of Hillel that his glory did not come from his authorship of the Mishna but from his ninety pupils, of whom "thirty were of a quality equal to that of Moses on whom the divine shekinah rested, thirty of a quality of Joshua for whom the sun stood still and thirty of a quality in between." Such was the glory of Alexander Gutman.

Hard on the heels of the tribute to Alexander Gutman came the two issues in volume 38 in honor of the twenty-five years as head of the department of psychiatry of M. Ralph Kaufman, whose place in American medicine and Mount Sinai historiography are equally assured. A masterpiece in clinical writing closes volume 38 in the form of the study of 1,200 patients with myasthenia gravis followed over twenty years by

Kermit Osserman and his co-workers and colleagues.

Volume 39 starts with a commemorative issue to honor Sadao Otani, small in stature but enormous in size in his devotion to pathology, to the hospital, and to his disciples. A major catastrophe to the hospital and to American medicine occurred in 1972 in the untimely death of Dr. Solomon Berson, the pioneer in the study of radioimmunoassay, whose co-worker was honored with the Nobel prize—which he would also have received had he lived. Please read the assessment of his achievements and his qualities in volume 39, page 327, as detailed by Dr. Dorothy Krieger and Horace Hodes. This blow was followed by the deaths at the height of their powers of Drs. C. K. Friedberg and William Antopol.

Volume 40 has a splendid monograph on membrane lungs by E. Converse Pierce and associates. A memorial issue to Dr. Solomon Berson edited by Dr. Dorothy Krieger covering the areas in which Dr. Berson's researches had been of seminal and germinal importance emphasizes the loss to the hospital and to medicine in his untimely death. In all, 1972 and 1973 were bad years; few hospitals or educational institutions could lose people of the caliber of Dr. S. Otani, Alice Bernheim, Solomon Berson, Asher Winkelstein, William Antopol, Charles Friedberg, George James, Isidore Snapper within two years without being mortally wounded.

It is a tribute to the vigor of the institution, the old hospital and the newer affiliated branches, that so much remained. A happy marker of achievement by a chief still in the vigor of health, vitality, and productivity is the appreciation of Morris Bender, edited by Edwin Weinstein, in the first 275 pages of Volume 41, with a tribute by his successor Dr. Melvin Yahr and contributions from friends and former pupils comprising the elite of modern American neurology.

Dr. George Blinik of the Beth Israel Hospital edits a memorial issue for Dr. William Antopol, who led a rich full life in pathology, who had a host of friends and pupils, and who generously shared his knowledge and the fruits of his knowledge with his colleagues. Dr. Antopol was responsible for the easy incorporation of Beth Israel into the Mount Sinai Medical School family and trod in both worlds, shedding light and largess in each.

Volume 41 notes with sadness, but also with pride and with joy of their accomplishments, the passing of Dr. Arthur Master, Dr. Arthur Touroff, Dr. Joseph Turner, and Dr. Alan F. Guttmacher. Dr. Guttmacher, as the whole world knows, was the fearless advocate of planned parenthood before it became respectable—a man of indomitable courage, of vision, of Christlike concern for all humanity, and with the genius of making his dreams become reality.

Midway in 1974, after five years as assistant editor and twenty years as editor, I decided that the time had come to pass the task and the pleasure of editing the *Journal* to younger, stronger, and more able hands. It was my pleasure to pass the duties on to the vigorous, far-seeing custody of Dr. David Dreiling, under whose aegis *The Mount Sinai Journal of Medicine* has expanded and bloomed. Dr. Dreiling has the rare gift of looking forward, of changing old familiar forms in favor of better ones. Under him the *Journal* has burgeoned and will continue to grow and prosper.

LESTER R. TUCHMAN, M.D.
Editor Emeritus

The Mount Sinai Journal: Future

The metamorphosis of the *Journal* from a publication devoted principally to case reports to a general medical journal has been detailed by Dr. Lester Tuchman in his ever-elegant way. Now, with one eye on the distinguished history of work published through the years that he has brought so vividly to our notice, I want to reiterate a gratitude acknowledged in the foreword to the *Journal's* first issue. Fifty years later, we continue to thank the Trustees and the Committee on Medical Education and Publications of The Mount Sinai Hospital for their continued moral and financial support.

This anniversary is an appropriate occasion to look back and, at the same time, look forward—like the Roman god Janus—to face the future as well as the past. When I was named editor-in-chief of the *Journal,* I had a dream for it that grew out of its forty years of service as a medium of ideas: to continue to provide our readers with refereed papers of cultural, educational, and clinical significance, to vary and enlarge the material published, to expand distribution, readership, and awareness of the *Journal* in the nation, and to publish the *Journal* monthly rather than bimonthly.

It has taken almost ten years, but now these goals are within sight. Since 1968 the *Journal* has been the publication not of one hospital, but of a large medical school complex, including five hospitals, a medical school, a school of basic sciences, and several smaller centers of learning. In this, our fiftieth anniversary year, I am pleased to announce the "nationalization" of the *Journal* with the affiliation to it of three institutions—Cedars-Sinai Medical Center, Los Angeles, California; Mount Sinai Medical Center, Chicago, Illinois; and Mount Sinai Medical Center, Miami, Florida.

These new affiliations will raise our number of reader-subscribers to 6,000, will afford a wider base for our panel of reviewers, will make available to the *Journal* a more varied source of material (our pages have been open to extramural papers for some two decades), will make distribution of the *Journal* truly national, and—last, but not least—will eventually enable us to publish monthly.

Later in the year, the *Journal* will be publishing a special issue commemorating these affiliations, presenting papers from each of the three affiliates as well as a history and description of each of them.

With this wider and more stable base of participation, our plans for the future also include:

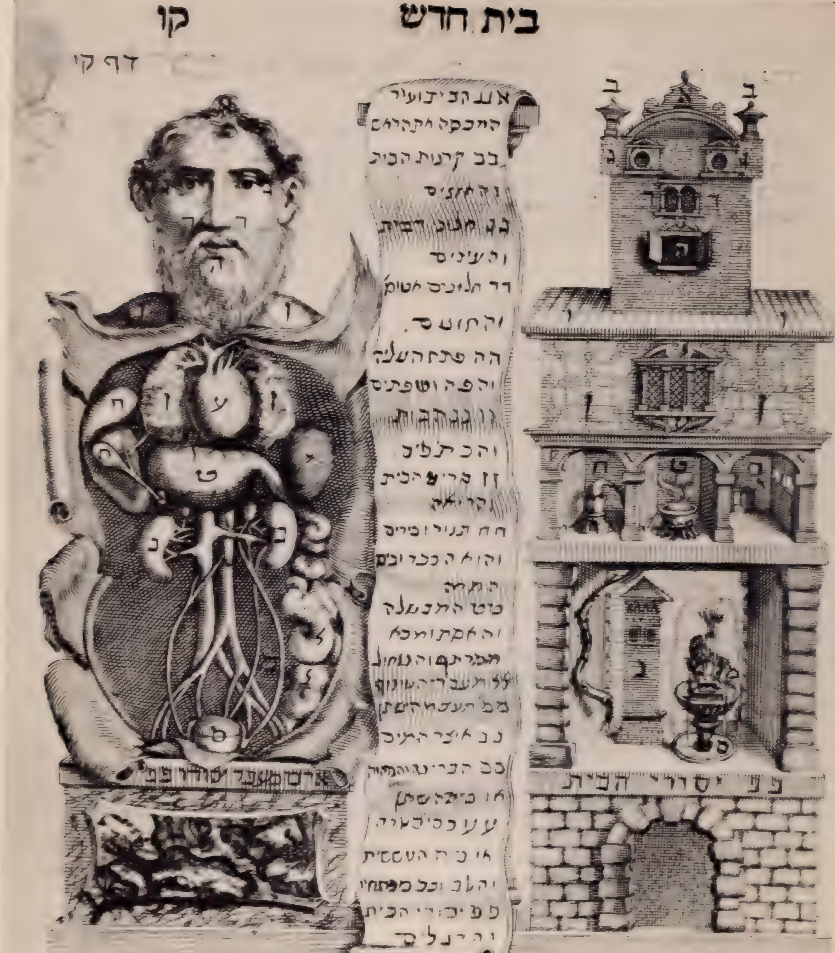
First, continuing to encourage authors to submit high-quality papers for refereed publication.

Second, expanding our special sections (Radiologic Notes was the first of these) to include the major disciplines and specialties. These sections will be dedicated to presenting useful clinical data and to updating the state of the art.

Third, addressing pertinent and pressing problems in basic science, clinical disorders, patient care, medical economics, and medical ethics in four or five annual monographs which will include clinician-oriented contributions from international authorities.

When I took on the editorship of the *Journal* in 1974, I said that I hoped the publication would serve as a medium of exchange between basic scientist and clinician, between student and educator, between medical school and graduate, and between medical center and community. Our aim for the future remains the same—above all, to make the *Journal* truly useful to all our readers, and thus to serve medicine.

David A. Dreiling, M.D.
Editor-in-Chief



This early eighteenth-century illustration is from the medicoreligious book *Masya Tuvya* ("The Work of Tuvya" or "The Work of Tobias") published in Hebrew in Venice in 1707 and written by Tobias Cohn, a member of the Cohen family of priests. It compares the human body to a house. The scroll in the center contains a key to the identifications on body and house. The eyes, for example, correspond to the windows of the watchtower, the ears to the watchtowers themselves. The heart and circulatory system are equated with the furnace which provides heat for the building, the stomach with the kitchen, where food brought into the building is made available for use. *Courtesy of The Jewish Theological Seminary Library*

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Medical Ethics: The Jewish Point of View

From an ongoing series of symposiums
Held each year beginning in 1978 at
The Mount Sinai Medical Center in New York City
Sponsored by The Page and William Black Post-Graduate School of Medicine of the Mount Sinai School of Medicine (CUNY) and the Committee on Medical Ethics of the Committee on Religious Affairs of Federation of Jewish Philanthropies of New York, Inc., Rabbi Isaac Trainin, Director

Introduction

A series of half-day symposiums entitled *Medical Ethics: The Jewish Point of View* were instituted in 1978 at Mount Sinai School of Medicine of The City University of New York. The purpose of these conferences has been to present important ethical dilemmas that now face the medical practitioner daily and to then examine where and how the Jewish tradition can contribute to a better understanding of these problems. Each symposium has been structured to include two or three problems, addressed in paired discussions by a physician who presents the medical aspects and then by a rabbi-ethicist who is a member of the Committee on Medical Ethics of the Federation of Jewish Philanthropies and who speaks for the Jewish view. Discussion periods follow.

The papers included here were derived from the first five symposiums, held from 1978 through 1982, either from edited transcriptions of the proceedings or from manuscripts prepared by the participants; presentations vary from formal to informal. Our thanks to the eighteen participants, both for their thoughtful presentation of complex and controversial problems and for their cooperation in preparing the manuscripts. We have not followed the chronological order of the oral presentations but have grouped the papers more logically by subject.

Why a symposium on medical ethics? Humanistic concerns have surfaced in medical decision-making and medical ethics as a discipline. Hardly a month goes by without a major medical journal publishing an article or presenting an editorial concerning medical ethics. For those of us who conduct teaching rounds, hardly a week passes in which we are not confronted by a house officer or a medical student insisting on a discussion of an ethical problem at the bedside.

Medical ethics once consisted of discussions of whether a doctor could advertise or share fees with colleagues and similar mundane issues. With the recent biomedical revolution and with the imminent prospect of even more dramatic advances, many more fundamental problems must be addressed. In addition to the headlined issues—euthanasia, abortion, genetic engineering, "test-tube" babies—day-to-day bedside decisions must be confronted:

- Who tells a patient what information, in what manner, and how much?
- Who decides triage problems in patient selection and the allocation of scarce resources?
- Who resolves the issue of confidentiality when an adolescent consults a physician about contraception, about abortion, about drug usage?
- When is a patient dead? when do physicians discontinue life-support mechanisms? how is the family involved?
- Under what conditions should we agree to withhold or offer treatment to "handicapped" infants?
- How do we in medicine weigh the risks and benefits of new or experimental treatment?

Can Medical Ethics Be Taught? Within the past ten or twenty years, valiant efforts have been made to introduce medical ethics into medical school curricula. R. M. Veatch notes, in "Medical Ethics Teaching: Report of a National Medical School Survey" (JAMA 1976; 25:1030), that by 1976 only 31 medical schools, about one third of all the medical schools in America, presented students with some type of formal approach to the teaching of ethics.

Ethicists such as K. D. Clouser ("What is medical ethics?" Ann Int Med 1974; 80:657), Veatch (*Case Studies in Medical Ethics*, Harvard University Press, 1977), and N. Fost ("Ethical issues in the treatment of critically ill newborns," Ped Ann 1981; 10:383), among others, have been writing steadily in the medical literature. Their purposes have been severalfold: (a) How to make ethics, a branch of theoretic philosophy, both applicable and palatable to the bedside clinician. (b) How to utilize the case method as a framework for the application of ethical methods. (c) How to use courses or workshops for more formalized exercises. (d) How to integrate into the decision-making process not only the physician, the patient, and the family, but also nurses, house officers, medical students, social workers, the clergy, ethicists, and, yes, even hospital administrators and lawyers.

These ethicists have also suggested the limits of their domain. They have pointed out that the ethicist can sensitize us, can make the physician and other medical personnel aware of the ethical implications of various activities and decisions. The ethicist can structure the issues by bringing hidden problems to the surface and by spelling out conflicting ethical problems, and can then propose orderly approaches to the ethical dilemmas that have been exposed. However, the ethicist cannot—except possibly in rabbinic tradition—be expected to produce a yes or no answer, nor can he or she be expected to act as a medical specialist or consultant and produce an outstanding diagnosis or solution to the problem.

Why the Jewish Point of View? Modern medical ethics has much to contend with: new and powerful drugs, highly complex technology. Added to the problems of the individual are the medical and health problems of our entire society. As human interrelationships become more complex, such medicine-related considerations as the food supply, housing, population control, and the ethics of the "lifeboat" have to be addressed. Therefore, medical ethics can use all the help it can get as it laboriously works its way into a discipline. What better aid can there be than the Jewish tradition, with its many insights into human behavior, its direct commentaries on health problems dating from the Bible and the Talmud, and the case histories in the writings and responsa of later rabbinic and medical authorities that elucidate ethical principles?

(Halakhah, "the way in which one goes," is the overall term for Jewish law. It rests first on the Bible, the written law. Second, it derives from the Talmud, the oral law, which consists of the Gemorrah and the Mishnah. These contain the commentaries of two thousand scholars dating from 450 BCE to 500 CE (about one thousand years) and consist of arguments, interpretations, and decisions about biblical statutes. Halakhah finally encompasses responsa, answers handed down by later great rabbinic scholars.)

Many talmudic and medieval Jewish scholars had joint professions as teachers, community leaders, and physicians. It thus behooves us to study and use their thinking and experience.

Moreover, medical ethical dilemmas can reveal the common ground among the great religions. And ethicists of different cultures and religions can bring to bear on medical problems the unique ethical and moral thinking, philosophic truths, and moral principles inherent in their traditions, which may have both theoretical and practical applications in medicine today.

Accordingly, we began this series of symposiums on medical ethics with the hope that problems could be aired, opinions voiced, and possible answers found. The papers in this issue reveal agreement and disagreement, among medical practitioners and between practitioners and Jewish ethicists. If we keep a dialog open and address the moral and ethical concerns of the complex biomedical issues that confront us, perhaps we can resolve some of our problems in the years ahead.

At the bedside level, it is rapidly becoming apparent that ethics committees in individual hospitals or hospital departments are a beginning approach. If the patient (or parent or relative when the patient is a child) sits down with the physician, the nurse, the social worker, the house officers, the medical students, and the clergyman-ethicist to air all the facts, emotions, economic problems, religious factors, and legal issues, a consensus will develop. Proper decisions will then be made for the individual patient.

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I. Beginning of Life

In Vitro Fertilization and Extrauterine Pregnancy ("Test-Tube" Baby)

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I am not addressing here the ethics of in vitro fertilization, but I am trying to outline the medical aspects of the problem and then raise the issues that can aid thinking about the ethical problems involved. Although at the moment the in vitro procedure seems to have only limited implications for ethics, in the long run I think in vitro fertilization will raise the most haunting of ethical and moral questions.

Medical Aspects

In England in July 1978, the first baby reported to be the result of extrauterine fertilization was born, and the report created a furor in the world press. Drs. Steptoe and Edwards, the two doctors who created the successful procedure, had been working on it for at least ten years prior to 1978. They had done a great deal of background research, their goal being to produce extrauterine fertilization resulting in a normal pregnancy. They have not yet published the scientific background and data of the event, although they have spoken about it at a number of meetings, so that I cannot summarize precisely what they did, only what they said they did.

Defining Who Can Be Helped. What exactly is involved? The event involved the use of the mother's ovum and the father's sperm, combining them outside the woman's body and then introducing the resultant embryo back into the uterus and letting the baby grow. Is there a need for such a procedure? Do we have problems that would require such help? The first point to consider is what benefit is gained by such a procedure. It is known that one out of six couples is infertile. Of people who are trying to conceive, after two years of trying 15% are unable to achieve a pregnancy. This is the group defined medically as infertile.

Infertility so defined may be caused by one or more of a number of factors. Forty percent of overall infertility is the result of factors affecting men. I exclude these factors as irrelevant to this discussion. The factors affecting women can be classified on the basis of the part of female anatomy affected: ovaries, uterus, cervix, vagina, and fallopian tubes. Physicians must examine each possibility and deal with those that are not excluded in a number of ways, choosing the route that suits each patient. Tubal causes make up almost 50% of the problems of infertility in women. Some of these tubal factors are correctable; most are not. For women with uncorrectable tubal causes of infertility, this new technique, in vitro fertilization, is the only route to fertility.

How does one select patients who might benefit from this procedure? Physicians must establish that the block to fertility is not in the man, must exclude disturbances in ovulation in the woman, and finally must establish that the only problem preventing fertility is that the ovum cannot get down the fallopian tube and meet the sperm, so that in vivo fertilization cannot take place. One way of identifying tubal problems is by a specialized x-ray procedure, hysterosalpingogram. Dye is introduced into the uterus and outlines the endometrial cavity and the tubes. An x-ray is taken, supplying a record of the findings. Normally, the fallopian tubes are very thin and about five to six inches long. The dye flows out of the fimbriated (fanlike) end of the tube into the peritoneal cavity. X-rays of patients who might benefit from in vitro fertilization show that the tubes are blocked. They may be dilated, showing the remnants of an abscess cavity which has destroyed the lining of the tube, precluding normal function; this is a hydrosalpinx. The x-ray may show a tube blocked because it is tied down in scar tissue, or

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may reveal the absence of a tube which was removed at surgery for a tubal pregnancy. The normal tube must be able to move freely to be able to pick up the ovum from the ovary. After x-ray identification of tubal disease, the woman may undergo diagnostic laparoscopy. By looking at the pelvic organs directly, the gynecologic surgeon can decide whether surgical techniques are available to correct the blockage of the tubes. Fallopian tubes that have been destroyed by infection cannot be rendered functional by any presently known technique. If correctable pathology is found, surgical attempts will be undertaken to repair the tubes. Patients of Steptoe and Edwards had previously undergone surgery to fix the damaged tubes, unsuccessfully. The cure rate for repairing tubal pathology is approximately 20%, leaving 80% of these patients infertile, in spite of major efforts to reconstruct the passageway between the ovary and the outside world. This is the group of women who can benefit most from in vitro fertilization.

Process of Extrauterine Fertilization. What are the procedures involved in extrauterine fertilization? Semen must be prepared—a more complicated procedure than simply putting semen in a test tube and adding the ovum. The sperm itself has to be obtained and activated. The surface of the sperm is altered when it passes through the uterus and into the tubes. Some of the surface material, the acrosome, is removed from the front of the head of the sperm, activating the acrosome which contains enzymes that disperse the cells surrounding the ovum, allowing the sperm to get to the surface of the ovum and penetrate it. The semen itself is not very useful. It took many years of research for investigators to discover the in vitro environment necessary for sperm activation. In fact, Steptoe and Edwards claim that little activation is necessary and a much shorter time is needed than had been previously used. All that is needed is dilution of the highly concentrated sperm in simple salt solutions. This offers no major problems. Today, semen is obtained and diluted on the day it is to be used.

What about the ovum? The ovum must be obtained at the single appropriate time it is produced each month. Since the late 1960s all hormonal data related to ovulation in normal women having normal menstrual cycles have been determined. All the details of the hormonal products of follicular development and ovum production have been identified. The essential feature in the cycle which heralds the onset of ovulation is a sharp rise in luteinizing hormone (LH), which occurs 12–36 hours before ovulation takes place. Before ovulation, the ovum has been changing and has started to become a fertilizable egg. Before all aspects of this developmental process were understood, it was difficult to obtain fertilizable ova. In early work on human ova, fertilization was usually unsuccessful. These ova had been removed from women undergoing surgery for other reasons. Often the ova were removed at the wrong time of the cycle, before the woman was ready to ovulate. Placing the ova in test tubes to mature did not result in successful fertilization. If the ovum is obtained after the rise in LH, it matures appropriately (undergoing meiosis) and becomes fertilizable. In each normal cycle, only one ovum matures in one of the ovaries. To obtain this ovum, the physician must identify the appropriate time of the cycle and operate on the woman. If ovulation has taken place, the tiny egg will be floating around the peritoneal cavity and will be destroyed. Using measurements of LH in blood or urine, the physician can identify the appropriate time for surgical removal of the preovulatory ovum.

Steptoe used hormonal identification of the timing of the cycle by getting daily morning urine samples and measuring LH on the same day. To do this, one needs a laboratory that works seven days a week and provides rapid analysis for the necessary hormones on the day the sample is obtained. The operating room always must be ready for the surgeon to operate at a day's notice to obtain the ovum when it is retrievable from the ovary, that is, before natural ovulation takes place, or within a 24–30-hour period of the start of the rapid rise of LH measured in blood or urine. Testart et al have recently shown a seasonal variation in the onset of the LH peak, which is in the afternoon in spring but in the early morning in autumn and winter (J Clin Endocrinol Metab 1982; 55:374).

Alternate Methods. Only one egg is ready to ovulate each month, often at an inconvenient time. The enormous expense in time, money, and emotional involvement is all focused on obtaining that single egg, which may not be successfully fertilized. Other methods of achieving multiple eggs, all ovulating at a previously determined time, have been tried. During the same time that techniques were developed to measure all the essential hormones in small quantities of blood, new therapeutic agents were discovered that could induce ovulation. It is now possible to treat a woman with clomiphene citrate, which is a competitive inhibitor of estrogen, in pill form. Such treatment results in stimulation of the hypothalamopituitary system to increase release of the gonadotropins, follicle-stimulating hormone (FSH) and LH. These, in turn, induce the ovary to develop ovulatory follicles, one or more depending on the dosage of the drug.

A human gonadotropin preparation containing FSH and LH (Pergonal) has also become available. This agent is given by injection and, depending on dosage, results in development of many ovulatory follicles. In these artificial cycles, a second hormone, human chorionic gonadotropin (HCG), which has biologic activity similar to LH, is given to induce ovulation. The timing of ovulation becomes predictable in these cycles, occurring 36–40 hours after the injection of HCG. Many developing eggs can be obtained in such induced cycles, increasing the chances of successful fertilization of some of them. A surgical procedure is necessary to obtain the ova from the ripened follicles in the ovary. After identification of the readiness of the follicles to ovulate, the woman is brought to the operating room and an operative laparoscope is used to look into the abdomen to find the ripened follicles. Other instruments are introduced into the woman's abdomen: a cannula to hold the uterus or ovary and a specially designed micropipette which is used to suck the egg out of the follicle. The ova are very small and cannot be seen. Only the large follicle (15–20 mm in size) can be identified and its contents emptied. Of course, this procedure requires that the woman be brought to a surgical suite, be anesthetized, and be operated upon. The patient must not get excited because emotional upheaval may alter her hormonal status after the procedure and reduce the success of implanting the embryo in her uterus two to three days later.

The retrieved ova are put into sterile containers or Petri dishes that contain the previously prepared sperm. Under microscopic control, the changes in the ovum that occur after fertilization can be observed. These ova are then moved to a new dish containing specialized support medium which was devised by years of work for this purpose. Steptoe and Edwards' group devised successful media for this phase of embryo development. The ovum begins to divide, becoming a 2–4 cell embryo by 12–24 hours after fertilization. When the embryo has attained 4–8 cells, the time has come for implantation into the mother's uterus. The hormonal events needed to prepare the uterus for implantation have taken place in the meantime. Only those embryos that appear normal under the microscope are used. Three or four of them are picked up by a micropipette and then squirted into the uterus. It is hoped that they will stay in the upper portion of the uterus and implant after floating around for about two days. Steptoe and Edwards tried it in 79 other patients but succeeded only in 1. Recent (1980s) data from many groups who are doing this procedure have shown successful implantation in only one out of five or six attempts. It appears that even under normal circumstances, probably only one out of four or five embryos becomes properly implanted, resulting in a pregnancy.

Ethical Issues

The overall procedure is not simple but is certainly feasible. Yet the costs are high, both financially and emotionally. What are some of the ethical problems raised?

Status of the Embryo and Parents. The U.S. government forbade research in this area in 1975, a move which eliminated any major financial support for research in human extrauterine fertilization. Most private funding sources agreed with the government's view. The Ford Foundation supported Steptoe and Edwards' efforts but did not fund similar work in the United States. However, from 1979 to 1983, at least a dozen programs were started to provide this procedure in the United States. The major reason for the lack of support related to the ethics of the procedure.

First, what is the status of the in vitro embryo? Agreement has been made in the United States that no embryos will be maintained in vitro for more than 14 days. Implantation is usually done 2½–3½ days after original removal of the ova. What does one do with the embryos that are alive but too numerous to be placed in the mother's uterus? (In 1983, from two to four embryos were being introduced into the uterus.)

Second, it is possible to freeze the embryo, maintaining its viability. What is the status of frozen embryos?

Third, who will be certain whose egg and whose sperm were actually used for any particular embryo? As soon as in vitro fertilization is done on a large scale, who will insure that the egg and the sperm are from the correct couple? Anyone who has worked in a large laboratory understands the complexity of this problem. Steptoe and Edwards were working under relatively primitive conditions. In that setting, they themselves knew exactly what was going on at each site. The more people that are involved in the laboratory, the more room there is for error.

Fourth, whose baby is being born? What if an embryo is placed in a surrogate mother's uterus? One daytime television soap opera character, a woman who had had a hysterectomy, insisted that her sister carry her embryo to term. There may be many women who do not want to carry a pregnancy for nine months because it is inconvenient. Should they be allowed to hire an incubator-woman to carry their embryo?

Genetic Engineering. A problem for the future is that the genetic material in the single-cell fertilized ovum could be manipulated by genetic engineering. This has already been achieved in bacterial systems. There is no reason to suppose that it would not be possible in humans. The DNA (chromosome material) from one individual's somatic cells could be introduced into the ovum, thus altering the characteristics of that fetus. This opens up the largest number of possible problems, to which thought needs to be applied.

Social Costs to the Ill. Finally: What is the social cost of this type of procedure? Can society support in vitro fertilization programs while denying other types of medical treatment to sick people? In a situation of limited resources, are we going to use scarce funds for in vitro fertilization to produce new lives, or should scarce funds be used to save the lives of people who are already living but are ill?

Medical and Social Benefits. Since this symposium was held, many new developments have occurred in this field. Many centers have started in vitro fertilization programs. Attempts to improve the success rate of this procedure have led to many important discoveries about early normal pregnancy. Thus, this procedure is now increasing our knowledge of the process of fertilization, early embryo development, and implantation. In the long run, these discoveries will help physicians treat many other patients who have infertility problems unrelated to the fallopian tubes.

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Rabbinic Comment: In Vitro Fertilization and Extrauterine Pregnancy ("Test-Tube" Baby)

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It is always difficult to separate the ethical concern that affects one system from the ethical concern that affects all systems. In vitro fertilization is a medical technological advance that presents a dilemma. To use biblical phraseology: Is this a case of "from all trees of this garden you may eat," or is this a branch of "the tree of knowledge from which you must not eat?" Which area is proper for human involvement? Years from now, will we reap, in unrelated areas, either benefits or difficulties from in vitro fertilization?

The first ethical concern is, Should a physician be involved in in vitro fertilization at all? Simply because physicians can treat a patient doesn't mean they may, or must, do so. Is infertility a disease that seeks medical solution? Of concern, of course, are the risks involved in the therapeutic approach. If there were no risks for the patient, no price to pay, then the procedure would be analogous to biting fingernails or overeating potato chips. These situations are well within the realm in which people may do things to themselves that may not be very good, but may not be too bad either. In biblical ethics, self-mutilation is itself a misdeed, an evil. It is forbidden for a person of sound mind to cause himself or herself injury. Even if there is no risk of fatality, the prohibition against self-mutilation is the same as the prohibition against mutilating somebody else. Ethically, I cannot injure another person, and I cannot injure myself; I am another person.

Minor and Major Risks. This interpretation has an ethical import broader than the question of in vitro fertilization. Statistically, the dangers of this procedure are not significant. Consequently, the question then becomes, Are the rewards sufficient? What is the risk-benefit ratio? Can the degree of injury that this procedure demands be justified? The procedure has implications exceeding those of cosmetic surgery, for example. Is infertility as significant a problem as a nose that didn't stop growing and is a few millimeters too long? A puffy bag under the eye greatly disturbs a patient. A person who is sufficiently disturbed by a condition that someone else could possibly disregard is nevertheless disturbed. A person who is psychologically disturbed to the point of requesting cosmetic surgery is certainly within acceptable risk-benefit ratios, as analyzed by ethicists, in accord with proper biblical tradition. After trying to dissuade the patient, a physician may perform such cosmetic surgery. Adequate ethical decisions have been made by now to clearly equate psychotrauma with physical disability and physiologic abnormality, although there is a major difference between a patient with a real abnormality and someone who would like to look like somebody else. No one would question a married couple who wish to become parents. Certainly such a couple would have justifiable reasons to undertake the minimal risk involved. The patient's decision-making is dominant in this case.

The second aspect is less clear. What about dangers that cannot be classified as minor injuries? What is the impact of the hormonal manipulation of the general physiology of the patient? What is the carcinogenic potential? What is the danger of causing a major medical problem? A number of women have been treated for failure to ovulate. The stimulatory hormones—human gonadotropins—have produced significant medical problems. These problems involve risks. Can

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a woman undertake these risks? Can a doctor subject a woman to these risks for the benefits to be achieved?

We deal with risks of unknown dimension. The danger of anesthesia per se is significant. It takes time to find the developing follicles. It takes time to remove the ova. The woman has to be kept under general anesthesia during this period. There is a risk factor with general anesthesia before you poke a hole in the belly. What is the risk factor and is it justifiable under these conditions? This is an ethical issue that still has to be analyzed. We don't know all the risks. It is difficult, since the process is new, to evaluate what the degree of psychotrauma is. Anyone who has counseled people with infertility problems knows the gradations in which these problems come.

Some patients enter the consulting room saying, as the Bible records Rachel saying to Jacob, "Give me children or else I will die." This presents one problem that has to be solved in which the risks to be incurred may indeed be larger than the benefits. If a woman is toying with the idea of in vitro fertilization but is also considering going to an adoption agency, and can't make up her mind, then the physician should encourage her to recognize the risks involved and not undertake this procedure. If they can satisfy their yearnings for self-fulfillment, for familial bliss, in any way other than the dramatic process of in vitro fertilization, they should do so. I think the question of risk should be put in its proper perspective.

There are obstetricians and gynecologists who do not hesitate to recommend pregnancy to a woman for whom delivery means a cesarean section, either for anatomic or some other reason. When there is no chance of natural delivery, with its lesser risk, physicians do subject the woman to anesthesia and to cesarean section. This risk has been accepted by our society. The risk of cesarean section is an adequate risk for a woman to take even if she has had three or four children and is not an infertile woman yearning for motherhood. Clearly, the risks involved in this procedure as now understood do not in any way negate the possibility of undertaking the procedure within an ethical system. When compared to the currently accepted standard of ethics, the risks of in vitro fertilization are no more unusual than may be incurred in the normal management of obstetric-gynecologic problems.

Experimentation or Therapy? A second, societal question also impinges upon the mother. Did Steptoe and Edwards do their homework? Any new medical procedure requires that question, that ethical probing. Is this human experimentation or is this therapy? Whether they did or did not do their homework is difficult to determine, since there has been a dearth of literature on exactly what they did. Nevertheless, it is clear they did not work on primates. From an ethical standpoint, is it proper to move from lower animals to humans without going through primate experimentation? When do physicians know they've done enough to make this leap of faith? For surely, whether it is a drug or an apparatus, when it is used in a human there is a leap of faith involved. Have you physicians done your homework?

If Steptoe and Edwards did their homework, as any prudent scientist would do, they determined the risks under our present state of knowledge. They determined what they know; more than that they cannot know. Medical research requires time for the research to get done and time for the researcher to analyze his research to know whether or not he can go clinical, can use his research on humans. If there is a woman pleading that she wants her baby—"if not I shall die"—then the move to clinical use makes sense. If not, something unethical was done.

Paternity. Another group of concerns may be uniquely biblical concerns in which society has left the Bible behind. I call these paternal factors. Semen procurement, in itself, is an ethical concern. Masturbation is looked upon in biblical ethics as an unethical, immoral act. To put a proper perspective on the many procedures for which the physician needs semen analysis, such as the workup of an infertile patient, consider the biblical attitude about masturbation, the concept of wasting of seed and wasting of ova. A procedure cannot be classified as masturbation if it involves not the wasting of semen but, on the contrary, causes the seed to perform its proper function, to impregnate an egg. There is no such thing as wasting of seed when a father presents his semen to a urologist for analysis after two years of trying to have a child to determine what prevents him from doing so. Even though this semen will not be used to fertilize an egg, it will take part in the process by which this husband ultimately, it is hoped, impregnates his wife. This use of semen is part of the "wastefulness" that God put into the process of procreation. Millions of sperm are liberated but only one sperm is needed. I have frequently counseled men whose sperm count is too low, or whose number of abnormal sperm is such as to make normal impregnation virtually impossible. It occurred to me that if you introduce the egg and the sperm to each other in an environment more conducive than the female reproductive tract, namely, in a Petri dish with the proper nutritional ingredients, it should be possible to salvage just one sperm.

The issue of legal paternity, however, does present religious ethical questions, especially to those who understand the religious consequence of knowing who your father is, the problem of consanguinity. What is the status of a child conceived by artificial insemination? The tumult on this issue is totally unwarranted. Taking a detour from the ovary to the uterus via a Petri plate doesn't introduce any new factors. In any honest analysis using biblical ethics there is no doubt as to the legal paternity of this child. A child conceived by artificial insemination is clearly the child of the one who donated the genetic material. There is no question on that issue, nor is there really much of a question concerning bastardy.

Status of Fertilized Ova. The first subject that I recall discussing at a Medical Ethics Committee meeting was the status of the fertilized ova in a Petri dish. What is the status of this embryo? It doesn't have any claim to humanhood. But from a biblical standpoint, a one-day post-conception child is entitled to all the ritual protection of the law. For example, Jews would be prepared to desecrate the Sabbath and Yom Kippur to save a pregnancy that is one day old. It is hard to know when a pregnancy is one day old, of course. Theoretically, potential life is sufficient to suspend all biblical prohibitions of working on the Sabbath, of eating on Yom Kippur. Jews certainly don't consider the fertilized egg as "nothing."

Upon ethical analysis, can we equate a fertilized egg in a Petri plate in the two-cell stage, or the four-cell stage, or the eight-cell stage with the same egg implanted in the uterus? Is it not a fair analysis to say that until the egg has been placed in that natural environment in which it can achieve its full potential, it should not be equated with an early abortion? Flushing the excess fertilized ovas down the laboratory sink is not committing an abortion. Such an act may not be equated with an early abortion, but it cannot be equated with "nothing." Here is an egg, now fertilized, that does have the potential to grow if implanted in a woman.

Donated Ova. What about the husband who has no sperm and the wife who has no ova? Can an egg be donated to them, keeping proper parental records? Is there any ethical responsibility to try to save at least some of the potential life in the egg? At this moment, the question has no great significance. There aren't that many eggs around. But if this process ever achieves mass production, then what Aldous Huxley described in *Brave New World* will be a reality. It is a problem that still requires much analysis.

Surrogate Mothers. Clearly, if there ever were a situation in which a woman wanted to incubate an egg, as an act of kindness to allow the woman who otherwise couldn't possibly conceive have the experience of motherhood, the act would be a charitable act. It would be a wise thing to do.

Dangers to the Fetus: Malformation and Publicity. But what is the danger to the fetus? The danger to the fetus comes from two points. One is malformation. There is much manipulation described in the medical procedure involved, from sucking up the egg into a micropipette, to popping it into a Petri plate, to moving it from medium to medium. Is this developing egg an egg in which every little point of that egg represents an organ system yet to be developed? What if you plop it on the wrong side? What will happen if you hit it too hard? Will you produce a monster? Will you produce an abnormal child? Ethically, this is an injury done to someone else. This is not the mother who says, "I'm willing to take the risk. You can poke a hole in my belly." If the fetus is granted humanhood (and Jews must do so), even a small risk of injury to another is morally unacceptable, unless there is benefit to the one who is carrying the burden of the risk—not a benefit to the mother or father, but a benefit to the fetus.

A little bit of talmudic logic to raise an issue—is it better to be born malformed or handicapped than not to be born at all? The risk to the fetus doesn't exist unless you do the procedure. This is an interesting problem. The first question is, Is it good to be born? If you say there is a goodness to being born, to achieving viability, then to achieve viability in a damaged state may be more valuable to the individual than not to achieve viability at all. If you follow the ethical principle, Do good with minimum harm, then the physician has done good to the fetus even if the fetus comes out malformed, without an arm, without a leg. Any other decision would also reach back into the abortion issue. If to be damaged is worse than not to be at all, then we have justification for destroying all damaged fetuses by abortion.

Because the biblical stand is clearly against such an approach, the question is, Is in vitro fertilization a significant risk to the child that doesn't exist unless someone assumes the risk of doing the procedure? The danger of malformation of a child must be evaluated strictly on a medical scale. Much work is done on infrahuman species. If the scientific consensus is that this type of manipulation is not significant, does not have a significant risk involved, no more significant, for example, than a mother smoking or imbibing an occasional alcoholic drink, then it should be done. The November 2, 1979 issue of *Science* contains an article detailing the toxicity of alcohol to the embryo. Is there now an ethical imperative prohibiting any woman from smoking or drinking during pregnancy?

There is good justification for us to say that a minimal risk is acceptable to our society. We don't live a cotton-swaddled life. We don't question each time whether or not we should cross the street or go around the block for fear of getting hit by an automobile. There are certain risks that adults take in their normal lives. Is the risk of in vitro fertilization within the range of normal risk?

The second risk to the fetus is publicity. In 1974 Edwards, analyzing the ethical import of the work he was doing, emphasized the evil done to the first child that would be conceived and brought to full term if there were publicity. (Edwards RG, Steptoe PC. Control of human ovulation, fertilization and implantation. Proc R Soc Med 1974; 67:932.)

What made him change his mind? Obviously, there are many reasons to change your mind on such a commitment—financial reasons, ego reasons. Clearly the problem of psychological and social maladjustment of the first children involved in this procedure must be weighed carefully.

The Yale project on the XYY gene type was stopped for this reason alone. People analyzed a project that was already ongoing and decided that the attention given to a child born with an XYY gene, which has been possibly implicated in a higher incidence of criminality, was injuring the child by the constant attention given to the testing program. The project could not be justified ethically.

I don't know whether any child will ever be exposed to the stares of the public that Lucille Brown's child will receive as the first child conceived by in vitro fertilization. If those stares are an evil, it is not justified by the thought that when we have a hundred thousand such children, people will stop staring. How about the first child, the second, the tenth, the twentieth? The publicity was an ethical goof and the goof was an intentional one. You don't call a press conference accidentally. Clearly the decision was made that the benefits to the child would be sacrificed for the sake of benefits to society, the parents, or the doctors. Unless there are psychological data that the glare of publicity is good for the child, those involved behave unethically. Scientific progress did not require the publicity to which the child was exposed.

Technology and the Domino Theory. The artificiality of in vitro fertilization is not an ethical concern. The idea of using an artificial method to help a woman conceive is of no ethical import. These days everything that is natural is good and everything that is artificial is bad, from your morning cereal and your soda pop to the organically grown corn and wheat that makes up your bread. We are not prepared to give up the advances of technology or declare that technological advance is bad for society. The claim of artificiality is, in itself, most complimentary to the genius of humans. Certainly, if a woman's problem could be solved by the artificial means of fertilizing her ova, there would be no ethical issue involved. On the contrary, it would be classified as a *mitzvah* (a good deed), and nothing more.

Our concern, however, is for societal ethics; and societal ethics are different from the preliminary one-to-one work done in the laboratory. Society has its own ethical standards. I refer to it as the technological domino theory, more commonly referred to as the "slippery slope." But leading to what? How do you turn it off? Incubator mothers, donor sperm, gonadal transplants—these are not things in the distant future. A good neonate ward can take care of any complication in an infant born after 30 weeks or so of gestation. Maybe physicians will soon be able to manage without that time restriction. Already an artificial incubator can make up for two or three months of the mother's gestation. Maybe we'll have a "test-tube baby" in the true sense, a baby conceived and raised in a test tube. There should not be any question about the humanity of the child or the paternity of the child; that is not the issue. If indeed one family's problem could be resolved by growing the baby in a test tube, if a woman without a uterus and her husband want to conceive a child and in vitro fertilization is the only way they can do it, I see no ethical import other than those already discussed.

But our society today seems to resemble *Brave New World* with a new cast of characters—Steptoe and Edwards instead of the director of hatcheries. A fact not known to many is that Edwards wrote about his social concerns in 1971 and again in 1974. Here you see the actions that follow a thought process. Edwards and Steptoe have been gestated by, they are the gestational product of, our society. They speak the language of our society. Edwards, in his 1974 article, never mentions the husband's sperm, but speaks of semen donors.

He questions whether donors are legally liable for "wrongful life" should the child come out of the womb damaged. He was not talking about solving the problem of a couple who want a child, but of solving the problem of society, which wants superior children. Why should I take my husband's sperm and make the same mistake twice? I chose him for a husband and a father. Now I could choose him for a husband, and someone else for a father. This concern applies not only to the question of in vitro fertilization but to the broader area of artificial insemination as well.

Of greater ethical concern is Edwards' statement that his work opens up the possibility of further work on human embryos in the lab, the possibility "of cloning them because in the early stages of early cell division, as you know, each cell has total potency. If each cell of this four-cell stage is separated, it will most likely develop into a full embryo. Thus, you can have quadruplets or quintuplets or hundreds or thousands of identicals. True cloning could go on, not by taking a somatic nucleus and sticking it into a female ovum, but by letting egg fertilize on two good contributors, egg and sperm, separated at the eight-cell stage. I could now have eight identical people who can be trained to do the work that I want to train them to do." (Steptoe PC, Edwards RG. Reimplantation of a human embryo with subsequent tubal pregnancy. Lancet 1976; 1:880.)

Since we can determine the sex of the blastocytes, can we then address the issue of sex imbalance in the population or parental choice of sex in a child? I quote Edwards again: "I could prevent the imbalance of the sexes by recording the sex of newborn children and adjusting the choice open to the parents." We suddenly have the master of the hatcheries, the president of the organization, declaring that if you want me to help you, you'll have to settle for a girl because my previous customer took a boy and I have to keep a balance. We're not talking about something that can be. This was a plan long before the first successful child was conceived in vitro.

Scientists have the right, indeed the duty, to open many doors. But they must be bound by the ethical and moral standards of society, not by the principle (to quote Edwards again), "push to the limit that is tolerable to society and let the lay attitude struggle to catch up with what the scientists can do. It is the job of the scientist to help society keep pace." This denies that science is bound by the ethics of society, declaring rather that society must catch up with the ethics of the scientist. This is the concern. No one person determines the ethics of society. If Steptoe and Edwards are not to our liking, we need not follow their ethical principles. We are not talking about science fiction and nightmares that might arise. These are the people who are working in the field. Their ethical perspective is unacceptable to us. The "slippery slope" is not a science-fiction nightmare. In biblical phraseology, it is the warning to Cain who was trying to rationalize killing his brother. Abel, his brother, was not eugenically desirable when viewed from Cain's vantagepoint. Thus he uttered the statement, "I am not my brother's keeper." God spoke to Cain: "If you do not do well, evil crouches at the door, longing for you, but you can master it." Cain couldn't master it; he killed his brother.

This is the whole story, constructive, active thinking that we all must, by divine command, open new doors. This is why God gave us our minds, with the insight to master nature. However, where potential for sin and evil lies in wait, there must be commitment to do well. To do well means to accept an objective yardstick of human morality, a yardstick that governs scientists and embryo alike. If we do so, we need not fear a "brave" new Huxleyan world, but can rather expectantly and eagerly await the contribution of multiplying technologies to the betterment of all.

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Abortion On Demand

JOSEPH J. ROVINSKY, M.D.

To me, this presentation is reminiscent of the surrender of the British to Washington at Yorktown. When the Redcoats marched out to lay down their arms, the British band allegedly played a tune entitled "The World Turned Upside Down." With reference to abortion, for me, the world is turned upside down. I would like to share with you a personal odyssey—a story of how one physician, trained for and concerned with the preservation of life and health, dealt with the question of the voluntary termination of pregnancy.

Medical and Legal Facts. The medical facts are clear. Termination of pregnancy is easy and safe. If it is accomplished with all of the modern medical safeguards, the termination of a pregnancy in the first three months of gestation is ten times safer for a woman than continuing through a normal pregnancy and delivery. The termination of pregnancy from 13 weeks onward is at least as safe as having a normal pregnancy and delivery. It is therefore a medical fact that abortion does not exact a penalty from the woman; on the contrary, if she makes the decision early and is aborted in the first trimester, her safety is enhanced. This is the reasoning that influenced the justices of the Supreme Court of the United States to arrive at the landmark decisions that today are the law of the land: that abortion is a matter for the woman and her physician to decide; that the state has no basis for intervening between the woman and her physician in the decision, or for regulating in any way the performance of first trimester abortion; and that in the second trimester of pregnancy, the state's only interest should be to insure the safety of the woman (so that it is permissible for state health codes to stipulate that the procedure be carried out in an appropriate medical care facility).

When Does a Fetus Acquire Rights? Obviously, if we all agreed that what is legal is justifiable, this discussion would not be taking place. Is an abortion, although legal, the taking of human life? If so, can it nevertheless be justified? I shall explore several different approaches to these questions.

Can a fetus be considered alive? Is a fetus entitled to the same protection as that afforded any living person? Very responsible people differ widely in their response to this question; the responses apply to in vitro fertilization and genetic engineering as well as to abortion, and answers that previously seemed at least pragmatically correct have been invalidated by technologic advances. A logical starting place must be the moment of conception, when male and female genetic materials unite and the potential for a new life is created. (I shall leave for others more qualified the pursuit of the question, When does the soul enter the conceptus?) Some people have argued that conception alone is not enough, and that the conceptus cannot be considered "human" until implantation occurs. This usually happens after seven days, on day 21 of a 28-day menstrual cycle, or about one week before the first missed menses. With sensitive modern radioimmunoassay techniques, a pregnancy can first be detected at this point. The woman first becomes aware of the possibility of pregnancy only one week later, when the expected menses fail to appear.

Various timetables have been suggested. One is that the fetus becomes "human" and assumes rights when it develops a human appearance (embryologically, about six weeks after conception). Another proposal is that, by analogy with the electroencephalographic criteria for brain death, the detection of fetal electrical brain activity be taken as a landmark (with modern techniques, this is possible about the eighth week of gestation counting from the last menses). In traditional

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Judaism, a conceptus of up to 40 days (close to seven weeks) has been considered to be nothing but an amorphous fluid (so that a priest in contact with a woman having an early abortion is not considered ritually unclean).

Temporally, the next possible criterion for the assumption of rights by the fetus could be fetal movement. With modern ultrasonographic diagnostic techniques, fetal movement can be detected as early as the eighth week of pregnancy. "Quickening" is usually detected by the mother between the eighteenth and twentieth weeks of gestation—a little earlier by some, and three to four weeks later by many. It is difficult for me to deal with a moral principle which has this much variability.

Viability, the ability of the fetus to survive if separated from the mother, has also been proposed as a criterion for granting rights to the fetus. Historically, a birth weight of about 1,000 gm, or a gestational age of 28 weeks, has been the outside limit. But pediatricians have confounded this issue with their improving ability to maintain a fetus alive outside the uterus. At present, we must deem potential viability to have been reduced to a birth weight of about 500 gm, or a gestational age of 20 weeks; theoretically, the lower limit of potential viability has not yet been attained.

In the United States, a fetus usually has not legally assumed the rights of a human being until it was born. Recent court decisions, however, have begun to award damages for injuries from external sources suffered in utero, so even this clear dividing line is becoming blurred. The Jewish tradition has similar elements of ambiguity. For example, if a woman is condemned to death for a crime, an incumbent pregnancy is not a deterrent to execution unless the patient has started labor, when execution must be postponed until after the baby is delivered. This suggests that the assumption of human rights by the fetus occurs with the onset of uterine contractions. To make the moral issue even more complex, there are cultures in which even after birth, a baby is not accepted as "human" until a certain time interval has elapsed, a name has been given, or certain formal rituals have been completed.

All of these lines of thought lead to the conclusion that to define "human life" results not in an absolute truth but in answers which change with time, culture, technical ability, and even with underlying motivation.

What Are a Woman's Rights? For the purpose of this dialectic, can abortion be justified even if we assume the "worst case"—that is, the earliest—definition of human life? It has been a popular argument that a woman has a right to control her own body and to determine her own use of her fertility. The opposite position may be that no person has a clear right to determine his or her own destiny if the fate of others is dependent on that decision. It has been adequately demonstrated that by not continuing with a pregnancy, a woman avoids a tenfold increase in risk of death—truly a significant price. To date, the fetus is dependent on the mother's body for its survival during at least the first half of gestation. Does a person depending for existence upon a sacrifice by another have a right to that sacrifice? In law and in medicine, that question so far has been answered in the negative. A patient requiring organ transplantation for survival cannot force a potential donor to cooperate. Further, it is traditional in Judaism that the life of the fetus and the life of the mother are not deemed of equal value until the major portion of the infant has been delivered. In early pregnancy, therefore, the dependent conceptus may be seen as threatening the woman in whom it resides with a significantly increased risk of death—in a talmudic sense, "pursuing" the woman—and repulsion of that threat must be permitted. Our argument has been developed thus far only in terms of physical risk; consideration of other pertinent matters, such as the psychological, emotional, cultural, and economic factors, only supports the position further.

We have arrived at the point at which I can defend to myself that any woman has a right to protect herself against the dangers of child-bearing, that such risks can only be assumed voluntarily, and that this position has traditional roots. But the ethical questions continue to march upon us in regiments. We have settled on the equivalent of what in law is called "justifiable homicide" to justify abortion. What should be our position if the risk to the mother can be eliminated without harm to the conceptus? Obviously, in very early abortion (for example, prevention of implantation, menstrual induction or extraction, or vacuum aspiration) we are withdrawing life support from a conceptus which cannot survive on its own or without our help. But with increasing gestational age, there is a greater possibility of fetal viability. Should late abortions be terminated by techniques which result inevitably in fetal loss, or should we attempt to evacuate the uterus so as to obtain a living conceptus, and then gestate the baby in vitro? What responsibilities for the baby does the woman retain in such a case? Should we accede to a woman's request for abortion for what seem to be frivolous reasons, for example that the conceptus is the wrong sex? Whether a different argument can be made for the conceptus with demonstrated anomalies I leave to Dr. Hirschhorn.

The Role of Society. We should pursue for a moment the question of whether society should be concerned with abortion regulation. Society does have an interest in the prevention of the taking of life for a number of reasons. First, killing poses the greatest possible harm for the victim, exacerbated by the anguish and apprehension that the victim would feel at the knowledge of the impending death, the suffering which takes place when life actually is terminated, and the unjust deprivation of what is a unique experience. Second, society is concerned because the act of killing is brutalizing to the perpetrator. Finally, society is concerned because the life that is ended exerts significant experiences of grief and loss on the family and friends of the victim.

How do these apply to abortion? Anguish, pain, and fear, reasons for protecting the victim, obviously do not apply in the early stages of pregnancy. Performed as a medical procedure and not as an illegal act, abortion brutalizes neither the physician nor the woman. There may be, even if only subconsciously, some feelings of grief and loss, but in unwanted pregnancy both the quality and quantity of damage to the emotional state of the woman (damage which after birth may be visited upon the child itself) are overwhelming considerations. A society's desire for population increase should not be enforced upon the bodies of its women. I, therefore, concur with the judicial decision that society's interest in abortion should be confined to insuring the safety of the procedure and to treating abortion equally with all other medical procedures. I can only strongly condemn any societal move toward promoting abortion as a means of population control or decreasing governmental fiscal burdens. I am cynical enough to suspect that "society" in the abstract does not always take its stand on the basis of morality or justice.

At the same time, one must not equate abortion with having a haircut or a manicure. It does pose professional ethical problems for the physician—problems which may differ with the age of gestation, the reason for the request for abortion, the circumstances surrounding the conception, and the condition of the conceptus. Such problems should be resolved privately between the physician and the patient. Neither the woman nor the doctor should be constrained by society in this decision. Both society and the health professionals must play a firm and active role in the proliferation and use of conception-control methods, to minimize as far as possible the need for abortion.

On this ethical basis, I can continue to serve the needs of my patients.

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Genetics, Amniocentesis, and Abortion

Kurt Hirschhorn, M.D.

When it became clear some ten years ago that prenatal diagnosis of genetic disease was going to be possible and readily available, the entire field of medical genetics did a complete spin. Prior to that time, the major form of genetic counseling took on a kind of racetrack philosophy, giving people odds on their having a normal or an abnormal child, depending on their previous history and genetic background. Basically, people were told to take these data and decide what kind of gamblers they were.

What usually happened was that a significant percentage of people, given these rather dire predictions of 25% abnormality, 50% abnormality, or whatever, decided it was bad to go ahead and get pregnant and did what they could to avoid pregnancy—something that, incidentally, was rather difficult at that time, and essentially illegal. Or, if a pregnancy did occur (and with the methods for birth control available in those days, unwanted pregnancy was frequent), women had an abortion. Most of the time, they got an illegal abortion, and the morbidity and mortality for illegal abortions was significant.

Today, a rather large number of abnormalities still occur; about two to three percent of pregnancies will result in children with major congenital abnormalities that cannot be detected prenatally. But with the availability of prenatal diagnosis for an ever-increasing number of genetic problems and, more recently, for developmental problems as well, a new option was offered to couples at risk when they took the risk of pregnancy: finding out whether they were lucky, or whether the fetus was abnormal.

One of the early arguments about the ethics of this option was formulated by Dan Callahan, director of the Hastings Institute for Ethics, Society and the Life Sciences, when he pointed out that we have to be careful about the term "option." Around the turn of the century, noisy and fume-producing new machines called motor cars were manufactured, and a lot of people argued that this invention was going to be the death of humanity. The motor-car manufacturer said, "Absolutely not, this is simply an option for transportation that we're providing. Nobody is going to stop anybody from using a horse and wagon." But—as Callahan points out—how many horses and wagons do you see around New York City these days? We now have to be careful about societal pressures in favor of the new medical options—on, for example, a pregnant woman who is over 35 and doesn't get a prenatal diagnosis; or on a woman carrying a Down's syndrome child identified by prenatal diagnosis who chooses not to have an abortion. This was the first specter raised when prenatal diagnosis, an enormously valuable, life-saving, and life-preserving technique, was introduced.

Chromosomal Abnormalities. The most common indication for amniocentesis is the risk of chromosomal abnormalities; for women over the age of 35, the risk of bearing a fetus with Down's syndrome or other chromosomal abnormalities is about 1.5%–2%. By the time a mother gets to age 45, risk at birth rises to about 5%–6%. The risk of discovering a chromosomal abnormality by amniocentesis is about double the risk at birth because a number of chromosomally abnormal fetuses are lost late in the second trimester by spontaneous abortion.

This age cutoff at 35 raises an immediate ethical question: since the total number of births to women over age 35 seems to be increasing, and at the same time a greater and greater percentage of children with Down's syndrome are born to women under age 35, we must ask whether we should be doing amniocentesis on all pregnancies, and whether we should selectively abort or avoid all births with Down's syndrome. Amniocentesis in all pregnancies is impractical at this time from

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the technological and the cost point of view, but the ethical question should be raised.

Among the X-linked disorders, one group cannot be specifically diagnosed in utero by prenatal diagnosis. If a woman is known to be a carrier, her daughters won't have the disease, but half of them will be carriers. Half her sons will have the disease and half her sons will not. The only thing we can tell that mother is whether or not she is carrying a male or a female. If she opts to abort males, she has decided that she is willing to abort even though there is a 50% chance of a normal male. Clearly, this is only 50% as bad as what a number of these mothers had done before we could tell them whether they were carrying a male or a female. They aborted any pregnancy, and thus had a 75% chance of aborting a normal child. Now this chance is reduced to 50% for a male child, but then 50% of all the pregnancies would be totally preserved.

Sex Preference. This brings us to preference for a child of one or the other sex, which some couples feel as strongly about as they would a child with a disease. There is the family that has seven boys and wants a girl. They just don't want another boy. Or the family that insists on a boy. Being the wrong sex is considered a sex-linked disease.

It is worth recalling John Fletcher's reason for disagreeing that determination of sex is not a reason for amniocentesis. (Attitudes toward defective newborns. Hastings Center Studies 1974; vol. 2, issue 21.) He in no way meant to recommend that it should be done. His point is that, currently, we accept the statement that our society, by means of laws and through our courts, has determined that the decision to have an abortion is something between a woman and her physician. The state has no business entering into this argument. If we allow this for abortion on demand, regardless of what the sex of the fetus is, where then is the logic or the ethics in interfering if the mother, in fact, wants a child of one sex or another, thereby giving that pregnancy a 50% chance of being preserved? Whether one agrees with this logic or not is an individual choice.

However, carry it several steps further. From time to time, we hear of a method using saliva, or vaginal secretions, or some other means to determine what the sex of an unborn fetus is. None of these methods are really practical at this point, but I don't doubt that one of these days they may be possible. If we combine this possibility of determining what the sex of the unborn child is without medical intervention, with abortion on demand as it now exists in our society's framework, aren't physicians really copping out when they won't tell somebody the sex of the amniotic fluid cells?

The principle behind this logic is compatible with the general principle that genetic counseling should be as nondirective as possible. In other words, the decisions and plans about a couple's reproductive performance must be their own. All that the geneticist can and should do is to provide them with a base of knowledge, with understanding of that knowledge, and understanding of the options available to them and the outcome of each option. To make an intelligent decision is the underlying principle of all medical genetics. Some people say that this attitude is a copout. But when directive versus nondirective counseling has been compared, it becomes clear that it is a good thing that counselors don't state their own opinion. If they do, it comes back to haunt not only them, but the family that has taken their opinion and valued it over something that they themselves might have come up with, which they could live with much better.

When Prenatal Diagnosis Is Possible. X-linked disorders such as hemophilia and Lesch-Nyhan syndrome and the autosomal recessive biochemical disorders or inborn errors of metabolism such as Tay-Sachs disease and over 100 others, can now be diagnosed prenatally. How do physicians select for amniocentesis? In the vast majority of cases, amniocentesis is performed because the parents already have an abnormal child. These couples know what they're dealing with; they come for a specific purpose. They don't want another affected child. Screening programs for Tay-Sachs disease, for sickle-cell anemia, and for thalassemia also detect couples at risk.

By screening, both the parents are identified as carriers. They have a 25% risk of having an abnormal child. They know that prenatal diagnosis is available. The ethical considerations in screening programs are dealt with in great detail in a number of publications. Again, I think the basic ethical thought came out of the Hastings Institute in 1972 and such provocative articles as Fletcher's "Ethical aspects of genetic controls" (N Engl J Med 1971; 285:776). Those guidelines have held up very well over the years. Some people still argue about whether a woman should find out if she is at risk before actually going ahead and delivering an abnormal child. Perhaps it is a matter of the person's sense of societal morality versus a sense of personal morality.

The autosomally dominant inherited disorders are particularly troublesome to me. A couple comes to a physician and one of them has a genetic disease. They realize that there is a 50% risk for a child with the same disease and request a prenatal diagnosis. It has become quite clear that a physician really has to discuss the situation differently with such a couple. Looking at the reality of this situation, the parents who have the disease are telling the physicians and themselves that they are not worth being alive. They basically intend to commit vicarious suicide because they think that an offspring who has the same disease, no matter what other qualities that offspring might have, is not worth bringing to life. Such parents need to understand this background very thoroughly before anything else occurs. If they don't, their later degree of guilt is absolutely unbelievable.

A variety of tools other than amniocentesis are now available for prenatal diagnosis. In the case of neural tube defects (anencephaly and spina bifida), if a set of parents has had an affected child, there is about a 4% risk of recurrence. If they have had two, there is a 10% risk of recurrence. One can make a diagnosis of an open neural tube defect by studying the alpha-fetoprotein level in amniotic fluid. This fetal protein leaks into the fluid to a greater extent in affected fetuses. One of the defects, anencephaly, inevitably is lethal in the newborn. Some of them are dead before they are born.

Spina bifida with meningomyelocele, however, is a variably nasty disease. Some of the defects are very small and closed. They won't even be detected by alpha-fetoprotein level. But many defects are severe and open and will lead to a quite difficult situation for the child and the family—mental retardation, hydrocephaly, paralysis, lack of control of urine and feces, and a whole set of gravely difficult problems for all. Women who have had one of these children generally don't want another affected child.

An experimental program derived from maternal serum screening of pregnant women for alpha-fetoprotein levels, which is virtually universal in England and in Scandinavia, is being experimented with in the United States. It presents many potential problems, since false positives and false negatives are created, and it has not been completely worked out. Certainly with the medicolegal atmosphere in this country, we are not ready for it.

Hemoglobinopathies. A great deal of work is now going on in the prenatal diagnosis of sickle-cell anemia and thalassemia. These are serious debilitating diseases common in certain ethnic groups, sickle-cell anemia primarily in the black community and thalassemia in the black, Mediterranean, and Chinese communities. It is now clear that physicians can diagnose these diseases prenatally with essentially 100% accuracy. Since some of these diseases are treatable, although treatment is difficult and many times unsuccessful, the basic ethical question is, what should physicians do if the disease is detected in the fetus? Should detection lead to a decision for abortion? It may or it may not. But should parents now be advised, as some people are trying to advise them, against abortion when the disorder is amenable to possible treatment? John Fletcher, writing on the ethical issues of prenatal diagnosis of the hemoglobinopathies, coined a phrase that I think is a particularly good one. The argument about treatment versus abortion should, in his opinion, not be extended to those who have the opportunity to avoid disaster—that being able to redeem disaster is certainly no grounds for seeking disaster.

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Teenage Pregnancies and Abortion

JOAN E. MORGENTHAU, M.D.

When Dr. Gribetz asked me to discuss the ethical issues related to abortion for the young mother, I welcomed the opportunity to reexamine my own position and the policy of the Adolescent Health Center of The Mount Sinai Hospital in this regard. However, I was frankly surprised when I realized that I was expected to talk on the subject of "Medical Ethics: The Jewish Point of View." My difficulty with the assigned title lies in the fact that I don't believe a sectarian point of view is appropriate to a physician's consideration of the abortion issue. I am a physician who happens to be a Jew, but I do not practice medicine as a Jewish physician. Obviously, one hopes that each physician seeks to develop a frame of reference for dealing with ethical issues, although formal medical training gives very little help in this regard.

A Nonmedical Issue. The issue of abortion—except when it is rendered moot because the fetus endangers the life of the mother—is, strictly speaking, not a medical issue. "Essentially nonmedical decisions should not be dressed in the mantle of 'medical' language simply because they require medical technology for their execution" (1). The role of the physician, as I interpret it, is to help patients achieve and maintain their maximum potential for physical, mental, and social well-being. To do this, the physician must acquire a constantly evolving data base of scientific knowledge, must evaluate this information in a critical and ethical manner, and must be prepared to apply what is learned—whether to a defined population or to a single human being.

Ethics Reflects Socioeconomic Issues. No particular religion, profession, culture, class, or sex should be thought of as having all the answers in the realm of applied ethics. I cannot agree with Rabbi Jakobovits' statement that "right and wrong, good and evil, are absolute values which transcend the capricious variations of time, place and environment" (2). My actions are predicated on my belief that, to a large extent, ethical precepts reflect the broader social and economic issues of the period in which they are articulated. If this is so, then in today's world the population explosion, the postindustrial society, the women's rights movement, inequality of access, and the ability to perform prenatal diagnosis are all factors which have molded our approach to the issue of abortion. Yet only the last of these can in any way be thought of as medical.

When I consider my role as a physician in dealing with the issue of abortion in the adolescent, I rely on the concept articulated by the World Health Association: promoting the physical, emotional, and social well-being of my patients. Each year in this country, more than one million 15- to 19-year-olds become pregnant, resulting in over 600,000 births. Most of these pregnancies are unintentional; yet approximately 90% of the infants are kept in the home by mothers who are ill-prepared for their parental role (3). What is particularly distressing is that the pregnancy rate for the younger mother, 16 years and under, is accounting for an ever-increasing percentage of the total. Our own studies at the Adolescent Health Center as well as national studies suggest that the younger teens are more likely to reject the abortion alternative (4). However, vital statistics suggest that, for the most part, it is abortion rather than contraception that exerts an ameliorating effect on the birth rate of the youngest mothers (5).

For me as a physician, the most disturbing aspect of these statistics is the magnitude of the very real problems associated with children bearing children. There are problems for the young mother:

> If she presents late in pregnancy, as is often the case, she has a poorer obstetrical performance than the older woman. She tends to have shorter birth intervals between children and will

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obtain a higher ultimate parity than women who start having children in their twenties (6).

Dr. Rovinsky tells us that we cannot equate money with life. While we would heartily subscribe to this in principle, in fact we know that there is an inverse relationship between parity and poverty and that two-thirds of all women who have their first baby before the age of twenty will be below the poverty level (7). There is a correlation between poor marital adjustment and early childbearing. The divorce rate has risen among all age groups, but it is three times higher when one spouse is younger than age twenty (8). There are problems for the infant of the teenage mother. In Iran this is reflected in an ancient proverb that says: "The first two are for the crows." While we no longer practice infanticide in the so-called developed countries, there is a definite increased morbidity during the perinatal and neonatal periods for those children born to teenagers. There is an increase in stillbirths and in prematurity. There is an increase in small-for-date infants, with all that this implies. Even taking matched cohorts for socioeconomic group, birth order, ethnicity, birth weight, and other important variables, there are physical, psychological, and social disadvantages over time for children born to mothers in their early teens (9).

Demographers tell us that we will never achieve a stabilization of our birth rate either in underdeveloped or industrialized nations anywhere in the world as long as people have as many children as they wish. In the developed countries, we can no longer rely on pestilence and famine to control population growth. One of our most difficult problems in the future will be how to reduce not only unwanted pregnancies, but wanted pregnancies as well, without violating basic human rights. I can conceive that in the United States within the foreseeable future one will need a license to have a child, or at least to have more children than society feels it can support.

Perhaps there will be some sort of an arrangement whereby anyone can have as many children as they wish, but beyond the prescribed number the parents will be "outside the system" and ineligible for social benefits. In other words, society may not be willing to support "excess" children. Think of the implications of this. One can argue that society today offers conditions into which a child has a right not to be born. It has been said that "it is morally indefensible to perpetuate conditions that handicap children from the moment they are born" (10).

The ethics of abortion focus on the inviolability of human life. Yet "human" is a philosophical, not a medical concept, and when life begins and when a life requires full protection are separate issues (11). Physicians must remember that their role is different from the role of spiritual advisor, lawyer, legislator, or philosopher, and must resist society's attempt or their own inclinations to miscast themselves in any of these roles. While patients press their physician to accede to an abortion for reasons that range from trivial to compelling, should the physician be the arbiter of any patient's degree of need? I submit there is no easy answer to this question. Even if the patient has the "right" to an abortion, the physician must never feel coerced into participation which goes against personal ethics. Some physicians cannot live with their conscience if they perform or even facilitate abortion; some cannot live with their conscience if they do not.

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Rabbinic Comment: Abortion

Rabbi David M. Feldman

I want to address some of the aspects of each of the three preceding papers from the Jewish legal-moral point of view. I think the best way to do so is to take a tack from Dr. Rovinsky's reference to the Supreme Court decision and describe an experience which I think illustrates some of the issues involved.

Does a Fetus Have Human Rights?

The Supreme Court, as you know, made its classic decision in January 1973, declaring that all statutes on state books against abortion should be stricken, that state anti-abortion laws were, in effect, unconstitutional. Six months before that, in July 1972, New York State, acting on its own, was among the first of the states to strike anti-abortion statutes from its books. Three months before that, I was called to testify in a court case on the subject. NOW, the National Organization for Women, not knowing that soon thereafter New York State would take this radical step on its own, took the state to court seeking to remove state laws against abortion. I was invited to testify on behalf of the plaintiff and against the state. What took place in the courtroom was an interesting scenario, because the attorney for the plaintiff made the unpardonable mistake of not clearing my testimony with her beforehand. Once I was on the stand, the following exchange ensued.

She asked, "Rabbi Feldman, do you not agree that the laws against abortion on the books of New York State interfere with your freedom of religion, your right to practice the rabbinate as you see fit?"

I said, "No," and she got all shook up. She said, "What do you mean, No? I read your book and I got the distinct impression that you would say yes."

I said, "You must first answer a prior question. First you must determine whether or not abortion is murder. If abortion is murder, then one cannot talk about freedom of religion. To illustrate, the Bible tells us that the ancient Canaanites used to practice child sacrifice. They would put a born child on the fire and offer it up as a sacrifice to Moloch. The Bible tells us such sacrifice is an abomination. Suppose these Canaanites were to be resurrected and were to come to America and wanted to practice child sacrifice here in the name of freedom of religion. Would we allow it? Of course not. Freedom of religion has no place here if it entails murder. We don't even allow polygamy for Mormons in the name of freedom of religion, we're certainly not going to allow murder. But if abortion is not murder, then we can discuss it, consider it. Then I will answer Yes to your question; the laws do interfere with my freedom of religion, because, as it happens, Jewish law has a different attitude in this matter. It has a more liberal stance. There are rabbinic responsa which would allow abortion for reasons other than a threat to the life of the mother. If I wanted to invoke these decisions I, of course, would not be allowed to because of existing state laws."

She heaved a sigh of relief, said ok, and pressed on: "Rabbi Feldman, do you not agree that our laws against abortion interfere with the rights of women, with the right of a woman to do as she sees fit with her body and her reproductive faculties?"

Again I replied, "No," and again she was disconcerted and said, "Do you mean No? I read your book and got the impression you would say Yes."

Again I said, "You must first answer that prior question. Is abortion murder? If abortion is murder, then you cannot talk about the rights of

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women, or the right of women to their bodies to do as they see fit, any more than you could say that a woman could take a 10-year-old or a 20-year-old person and say, 'Look, you are the fruit of my womb,' and shoot him dead because he happens to be from her body. If those who claim abortion is murder are correct, then the situation before birth is equal to the situation after birth. The woman's rights, that is, the right to her body or to control her fertility, cannot be considered. That a fetus comes from her body makes no difference; she could never murder the product of her womb. But if abortion is not murder, we can discuss the matter. Then I would say, 'Yes, you're right; the law does interfere with the rights of women from the standpoint of Jewish law,' because Jewish law is even more concerned with the welfare of women than the National Organization of Women would call for. In Jewish law in the matter of abortion, it is not the husband, it is not the fetus, it is not 'right to life.' It is none of these things. It is the welfare of the woman that is primary. *Tza'ra d'gufah adif:* 'her welfare comes first.' In all matters of birth control, sexual relations, or abortion, the welfare of the woman is primary. Once we declare that abortion is not murder, only then can we take into consideration the welfare of the woman. Her welfare is primary in a situation in which there is a clash between the fetus' potential life status and her actual life status."

Primacy of the Woman's Welfare

The Jewish emphasis on the welfare of the woman, our determination that maternal indications are more decisive that fetal ones, continues to get us into trouble. The question of whether an abortion is permissible under the circumstances of the Tay-Sachs disorder has been raised. Some members of the medical ethics committee of the Federation of Jewish Philanthropies are opposed to abortion even for Tay-Sachs and, therefore, are opposed to amniocentesis to determine whether the fetus is indeed afflicted with Tay-Sachs. The reasoning is that amniocentesis is an intrusion, an invasive assault on the womb for no purpose, for no sufficient reason, because the only thing anyone can do with a Yes answer is have an abortion, and abortion is not allowable for fetal indications, only for maternal indications.

Summarizing Jewish law on abortion, historically, legally, and morally, I have come to the following generalization: the welfare of the woman is primary; therefore, maternal indications warrant an abortion, fetal indications do not necessarily warrant it.

To illustrate: If a woman were to come before a rabbi and say, "I took thalidomide [or: I had German measles during pregnancy], and there is a 50–50 chance that the fetus will be deformed and, therefore, I want to have an abortion, because what kind of life is that for a child?" the rabbi would say, "You can't do it. First of all, how do you know he's going to be in the fifty percent that's going to be deformed? Secondly, if he is in the fifty percent that's going to be deformed, how do you know that that kind of a life is not worth living, that it's better not to be born? You don't know that. *Bihanei kavshei d'rachmana lama lakh:* 'Don't mix into the secrets of God.' " However, if the same woman, in identical circumstances, came to the same rabbi—you're not allowed to shop around for a rabbi who will give you the right answer—and phrased the question differently, saying, "I took thalidomide [or: I had German measles], and there is a 50–50 chance that the child is going to be born deformed, and that possibility is driving me to mental anguish," then the rabbi would say, "Go have an abortion, you poor woman."

Posing the case the first way is talking about a fetus and what may happen. There you don't know. That is future, that is potential, that is hypothetical. But posing the case the second way is talking about what is, and talking about a woman; and in the halakhic view a woman has prior claim to ensure that her well-being, her welfare, is protected. Therefore, a woman claiming mental anguish—that is, severe mental anguish—is a maternal indication.

In the matter of abortion when Tay-Sachs has been confirmed in the fetus, the answer lies in how you see the question. If the prospect of early death for the infant is causing severe anguish here and now to the mother, a fetal indication becomes a maternal indication, since Jewish law ranks this sort of mental well-being on a par with physical welfare.

According to the dominant position in Jewish law on abortion, seeing the matter in terms of maternal considerations is necessary. But there is a more lenient minority opinion that is satisfied with certain fetal indications alone. Rabbi Eliezer Waldenberg and Rabbi Shaul Yisraeli of the Jerusalem rabbinical court have said that in some cases, fetal indications are sufficient to warrant abortion. If you choose not to follow them, the burden of Jewish law is on the side of maternal reasons even in this case. Incidentally, the Catholic public health chief in Detroit adopted as public policy for that city what is essentially the rabbinic view. Abortion is to be based on maternal indications because that is ground more solid than fetal indications, which are essentially risky as a basis for decision.

Is Abortion Murder?

These views are possible, however, only if abortion is not murder. If abortion is murder then it cannot be resorted to even to save the life of the mother. In Judaism, murder is one of the three cardinal sins—the others are adultery-incest and idolatry. One has to choose martyrdom rather than commit them.

Another point of view declares abortion to be worse than murder. The Catholic Church, aside from its public policy protest against abortion as murder and, therefore, objectionable to all people, takes the position theologically that abortion is worse than murder because it destroys the eternal soul.

When Does the Soul Enter? Dr. Rovinsky left it to others to discuss the question of when the soul enters. I, too, leave it to others, except to take note of the role it plays in the thinking of some.

I once told a conference on abortion, "For two days you've been asking when does the soul enter: at conception? at first trimester? at birth? That's not the issue; it's monumentally irrelevant. From our standpoint—the Jewish standpoint—the issue is, What kind of a soul? Classic Catholic theology teaches that the soul that enters is a tainted soul. This presupposes the idea of original sin, that Adam and Eve sinned—not with an apple, but with lascivious sex. Because of that, they brought all of humanity down from grace. Not only did they sin, but all of us inherited that sin: 'in Adam's fall, we sinned all.' Also, there's no way to wash away that original sin, say by good deeds, except by baptism with holy water."

In the sixth century, St. Fulgentius declared that the tainting of the soul takes place at conception. This explains why the Church has taught that if there's a difficulty in childbirth and mother and fetus threaten one another, preserve the fetus and let the mother die. The Church is not being cruel—merely consistent. Its consideration is that the mother, who is perhaps twenty, perhaps twenty-five, has presumably been baptized as an infant. So let her die and go to her reward in heaven; but if the fetus is not brought to term and baptized, it will suffer perdition. From this theological standpoint, abortion is worse than murder because it consigns the fetus not just to death but to hell, to death in both worlds.

Hence, in the nineteenth century, Catholic theologians at the Sorbonne invented a baptismal syringe wherewith to baptize a fetus in utero. In the case of a miscarriage, a spontaneous abortion, they put holy water into the syringe and baptized the fetus in the womb. This shows consistent concern for the spiritual welfare of the fetus—stemming from a set of considerations entirely different from the approach to abortion of the Jewish community, considerations that Jews cannot share. Jews don't have this concern with the original sin of the soul.

The Talmud gives several almost whimsical answers to the question of when the soul enters the body. Perhaps the soul enters at conception; perhaps at first trimester; maybe at birth. In the Talmud, one rabbi suggests that the soul enters when the child says Amen: You say a *b'rakhah* (blessing), and the child answers Amen; that's when the soul enters. But after discussing these possibilities, the Talmud dismisses the question with, "Don't mix into the secrets of God." We don't actually know when the soul enters, nor is the timing relevant. The Talmud says—in words which Jews quote in their prayers every morning—*Elokai n'shamah she-natata bi, t'horah hi:* "My God, the soul that thou hast given me is pure." Now if the soul is pure and not tainted, then one really could whimsically say that the earlier an abortion, the better. Send the soul up to heaven before the child gets a chance to sin and contaminate the soul. This would be in keeping with the Jewish idea that we contaminate our souls by our own sins.

Abortion is a human, earthly question for the earthly court to decide. Is feticide a homicide, or not? The answer to that has got to be No, because if it were Yes, abortion couldn't be performed, even for the gravest reasons. But if feticide is not homicide, then you may do it for the woman's life, for the woman's health, for the woman's welfare; or sometimes, for the welfare of an existing infant. These are some of the laws that have been given in responsa by rabbis through the generations.

If abortion is not murder, what are the guidelines to help us understand the Jewish attitude? A very important mishnah in Oholot in the Talmud tells what to do in case of a difficult pregnancy; one must dismember the fetus limb by limb "because her life takes precedence over its life." That's true all the way through the pregnancy until the moment of birth. Then comes the second half, the more illiberal, harsh side, of the mishnah. It proceeds to say *yatza rosho,* "if the birth process has begun, if the baby's head has emerged" (or, to be precise in the case of a breech birth, if 50% of the baby has emerged) then, in that case, *ein nog'in bo,* "you can't touch it," *she'ein dohin nefesh mip'nei nefesh*—because now you have a human life. Until then, you didn't have a human life, but now you do. You cannot "set aside one life for another." This doctrine, by the way, has very interesting implications for the whole question of wantedness and quality of life, recognizing a difference between the mother, who has a husband and other children and associations, and the child, who has none of these. But the child does have life, and once the child has human life, then it is equal to that of the mother, with all her associations, with her husband and children depending upon her. Life is infinitely precious; you can't touch it. Up to the moment of birth we're dealing with potential human life. You have to treat it seriously; you have to protect the fetus and its rights; but it is still not human life.

"Life" and "Human Life." I must disagree here with the doctors, because the biologists and the physicians can tell us when life begins, but not when human life begins. This is essentially a metaphysical question. The Catholic metaphysical tradition has given us its answer; the Jewish metaphysical tradition is that human life begins at birth. Before that, there is potential life, and it is life, but not actual human life. Jews do not deny that animals have life. Nonetheless, we allow ourselves to slaughter and eat them. Even plants have life. Let's not confuse life with human life. Human life is an arbitrary declaration of a philosophy, of a metaphysical system. We say human life begins at the moment of birth. "Right to life" is now the slogan which anti-abortionists have taken for themselves, but it is one of those slogans that misleads. We are not dealing with the right to life when we talk about abortion. We are dealing only with the right to be born. The right to be born is far different from the right to life. Once that baby exits, once just the head emerges, the baby has a right to life which cannot be compromised. Then the Jewish tradition will be the first to protect it and say, This is life in the absolute, indivisible sense. Until then, we're not talking about the right to life, but about the right to be born. Otherwise, why choose this particular point in the gestational continuum?

In a hyperbole, the Talmud says the person who doesn't marry is guilty of murder by not bringing children into the world. The Talmud is, of course, speaking allegorically; otherwise, if on a certain night a woman were to say, "I have a headache tonight," or if a man left town for a week, they could be hauled into a Jewish court for murder because a potential child was not conceived. Do we call it murder at that stage? A little later? The reproductive decision can be made at the first and at the later stages. The decision to become pregnant is not that different from the decision to remain pregnant—but only up to the moment of birth. Then the right to life is important. The right to be born is important, but it is secondary to the welfare of the woman.

My Own Stance. I have, nonetheless, taken a position against abortion because abortion as a reproductive decision is different. On June 30, 1972, the day before abortion became legal in New York State, a doctor appeared on television to say that women should get used to the idea that an abortion is no different from a tonsillectomy. This is part of my target; to emphasize the difference, to avoid any notion of casualness regarding abortion. So I have joined forces with those conservative voices in the community who disallow abortion except for the gravest reasons, such as a threat to life, though that's not what the more liberal Jewish legal tradition provides. It's important to remember how my stand developed. Our mothers and grandmothers who came to the rabbis and asked questions about abortion spoke from an entirely different mental set. They were women who, if they had three children, knew that the fourth child would go without shoes, but it didn't matter. Money was not a factor.

The Question of Money. I have to address myself to the question of money in capital cases, in cases of life, in response to Dr. Rovinsky and Dr. Morgenthau. The equation is just not as direct as it appears. It would seem that if you can't afford it, you shouldn't have a child, and if you have children you are increasing poverty in the world. That's a simplistic view of the entire matter. In fact, it is affluent people who are deciding to have fewer children. They would rather have a second car than a third child, or a bigger home in the suburbs than another child. It's the affluent who are not having children, but the poor who are having more. That's where the word *proletariat* comes from (*proles,* "offspring")—the proletariat are prolific.

A poor black woman in Boston declared, testified, that she wanted her child because she was poor. She said, The child is an inalienable part of me. If I have a child, I know no one can take it away from me. That evil society out there, which has decided that the rich will have money and I am to be deprived of opportunity, cannot take this away too. In other words, she wanted a child because she was poor; others don't because they're rich and spoiled. Those parents of ours, mothers through the generations to whom the rabbis addressed their responsa and from which the Jewish standpoint was developed, had a mindset in which life was precious and they had reverence for life. They did not measure children with the coin of finance. To them the rabbis could say: Strictly speaking, abortion is not murder; but it is still something you shouldn't do unless you have correspondingly good reason. If you're a woman who approaches the matter with gravity and seriousness, then the answer is that you can decide on the basis of severe anguish or similar grave reasons of welfare. But if you're a woman who would use abortion as a backup to faulty birth control, or as a matter of course for economic reasons, the philosophic rather than the legal Jewish tradition must be brought to bear, stressing reverence for life and even potential life. The alternatives must be sought first, especially in view of medical advances with respect to maternal or fetal complications, and especially in view of the wantedness of children by adoptive parents. Abortion should not be forbidden, but its moral, theological, and social consequences should be taken seriously as part of the basic prolife stance that we all share.

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The Infant: Right to Privacy and Patient's Right to Know

Irwin Krasna, M.D.

Any pediatric surgeon encounters daily the ethics of decision-making related to infants and their parents—especially decisions about performing life-saving surgery on an abnormal infant.

As a pediatric surgeon, I am often called upon to operate on a child who is born with a host of abnormalities, one of which may be life-threatening. A common example is a baby with Down's syndrome born with duodenal atresia, a blockage of the intestines that can easily be corrected by an operation that takes an hour or an hour and a half of the surgeon's time. The blockage can easily be bypassed, and the child's prognosis for leading a completely normal life from then on is excellent—except for the fact that the child has Down's syndrome. Physicians are often confronted with parents refusing to give permission for surgery, saying that if the baby has an obstruction and will die without the surgery, the death would be a blessing for the baby as well as for the family.

Surgeons often see a baby with meconium peritonitis or meconium ileus, an abnormality in the meconium accompanied by a bowel perforated before birth. The child is born with a massively distended abdomen and intestinal obstruction and, unless surgery is performed, the child will starve to death or die of peritonitis. If surgery is performed, the surgeon is saving a child who has cystic fibrosis, since all of these children have cystic fibrosis. Often the parents say, "I don't want a baby with cystic fibrosis. I don't want to have a baby for whom I'll have to have a pump in the house, a nebulizer and an oxygen tent, a baby whose best outlook may be to live to be 17 or 18, and then die of lung disease."

A baby born with a myelomeningocele is another example of this dilemma. If the child is not operated on, the exposed spinal sac, the meninges, will become infected and the child will die of meningitis. If the child is operated on and the sac is covered with muscle and skin, meningitis is no longer a risk, but many of these children will develop hydrocephalus within a few weeks of surgery, and many will be unable to walk unaided or to control bowel and bladder normally. Neurosurgeons often either refuse to operate on these children or advise the parents that they should not give consent for surgery. Probably less than 25% of these children can hope to avoid further problems and lead a normal life after relatively easy surgery. It is often difficult to predict what the future outlook of a one-day-old baby will be.

Still another example is the older child with a malignancy, a neuroblastoma, many of which cannot be completely removed by surgery. Radiotherapy and chemotherapy may achieve a favorable response but such children often eventually die. Is it ethical to try to achieve a cure or to prolong the child's life, even though chemotherapy treatment is costly, risky, and debilitating and causes the child to lose his hair? Or is it in fact kinder to say, "Let the child die without suffering or the torture of treatments, blood tests, and blood transfusions?" Should we physicians operate on these babies and children, or should we not? Should we let the baby die unattended, because the parents want us to, or should we do the things that we, as surgeons and physicians, know how to do best, thus permitting the child to live? Whatever we decide is undesirable. Does the family have the right to a choice? Do I, as the baby's surgeon, have the right of choice? Do I, as the baby's surgeon, have the right to an opinion? Everyone has the right to life, liberty, and the pursuit of happiness. Think about the baby's right to live. Think about the family's right to happiness without this tragic creature ruining their lives.

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What about my liberty as a surgeon to do what I think is right? And most pressing of all, what about the baby's rights to all of these things? The baby cannot speak for itself. We adults, as surgeons, as administrators of hospitals, as parents, are making the decision for somebody who cannot make a decision. Doesn't the baby have a vote in the decision? To decide that a Down's syndrome baby's life will not have worthwhile quality and that therefore physicians should not bother to put in two hours of surgery time and take care of the baby for two or three weeks afterward is quite different from the case of an adult who has a terminal disease and prefers not to be treated.

Pediatrics, the journal of the American Academy of Pediatrics, in a 1977 supplemental issue on ethical problems, reported on answers to twenty questions by members of the American Pediatric Surgical Association and chiefs of pediatric services (1). Some of the questions were as follows (with percentage responding to each alternative):

> You are referred an infant with duodenal atresia and Down's syndrome. The parents are indecisive about consent for surgery. You would (check one):

(a) Refuse to operate even with full consent and refer to another surgeon.	1.1
(b) Move them in the direction of not signing, making the decision to let the baby die on your own; however, if they desired surgery, you would do it.	23.6
(c) Try to provide them with all known facts about the infant's condition and then tell them you will respect whatever decision they make, but the decision is completely theirs.	51.7
(d) Try to persuade the parents to allow surgery but not take them to court if they refuse.	16.5
(e) Get a court order directing surgery to be done if the parents refuse to sign consent.	3.4

> Would you acquiesce in parents' decision to refuse consent for surgery in a newborn with intestinal atresia if the infant also had:

	Yes	No
(a) Down syndrome alone?	76.8	19.1
(b) Down syndrome plus cyanotic heart disease?	85.0	10.9
(c) Anencephaly?	95.9	0.4
(d) Cloacal extrophy?	64.8	29.6
(e) Meningomyelocele?	60.3	28.5
(f) Multiple limb or craniofacial malformations?	62.5	29.6
(g) 13–15 trisomy?	86.5	5.2
(h) No other anomalies (normal aside from the atresia)?	7.9	88.4
(i) There is no situation in which I would accept such a decision	3.0	

Interestingly, when these pediatricians were asked the personal question "If you were the parent of a newborn baby with Down's syndrome and intestinal obstruction, would you consent to surgery?" more than one-quarter (27%) said they would give consent to intestinal surgery; 66.7% said they would not consent.

Another question in the survey was as follows.

> If you agree that under certain circumstances it is permissible to allow certain severely damaged infants to die by withholding surgical treatment, number the following criteria for making such a decision in order of priority (most valid as 1, least valid as 5).

The response was the following ranking.

1: Potential quality of life (as child and adult).
2: Possible adverse effects on the family (psychological, social, financial).
3: Infant's probable I.Q.
4: Cost to society (hospital care, institutionalization, special therapeutic program).
5: Parents' willingness to raise the child at home.

Thus most of the pediatricians surveyed felt that what made them arrive at the decision to withhold treatment was the potential quality of life.

The decision not to perform life-saving surgery on these children is chosen because we adults, we physicians, do not believe that the quality of life that the future holds for this child is worthwhile. In other words, the only worthwhile quality of life requires normal intelligence, acceptable physical appearance, ability to walk unaided, possession of a full head of hair. Any child who cannot meet these standards is not worthy of our efforts at resuscitation or our paying money for lifelong care. The problem with this reasoning is Where do you draw the line? Is it below-normal intelligence? severe physical handicap? unpleasant face? Does this reasoning mean that a grotesque child of normal intelligence should be permitted to live, but a child who is also retarded should not be permitted to live? Or do we physicians say that all grotesque children will not have an acceptable quality of life, but plain or ugly children deserve our care. Do we physicians work hard on a baby with a giant omphalocele who will eventually be a handsome boy, but not operate on the unattractive baby born without forearms?

Is drawing the line a question of length of expected survival? Do we work hard on a child with cystic fibrosis because he or she may reach adolescence, but let children with trisomy die of an imperforate anus or TEF, because their life expectancy is usually measured in months? What about a baby who has had 90% of its intestine removed because of gangrene or Hirschsprung's disease? With hyperalimentation, the baby can live a few years, but will ultimately die of short-bowel syndrome. Do we only work hard on those babies who have a chance to ultimately recover, or should a year or two of life be worth striving for and worth using our financial resources to achieve?

Another serious question revolves about the definition of "heroic measures." Years ago, kidney dialysis and coronary bypass were considered heroic measures. Today they are both routine medical procedures. Is implanting (under novocaine anesthesia) a Broviac catheter to give the baby total parenteral nutrition "heroic," or as routine as a daily bath or taking a blood count?

Where should the line be drawn for the Down's syndrome infant with a surgical problem (2, 3). If a physician believes that "heroic" neonatal surgery should not be performed on a Down's infant, what about a six-week-old Down's baby with pyloric stenosis? Should we physicians let this baby die of vomiting or dehydration because it has funny eyes, an unusual crease of the palms, and is not going to grow up to be very smart? What about a ten-year-old Down's child with appendicitis? Do we let the appendix rupture or do we perform an appendectomy? Would any decent human being who sees a Down's child in the path of an oncoming truck not warn him of the danger or try to save him? What if this child were hit by a car and had a ruptured spleen—would anyone ever consider letting the child bleed to death? Why is a two-day-old helpless infant different? I don't believe there is any difference between active and passive euthanasia.

The purpose of euthanasia is to kill a person, and no matter how it's done, the purpose is still to permit the baby to die. Refusing to do a colostomy on a baby with an imperforate anus, with multiple congenital anomalies, or refusing to do a bypass procedure on a Down's baby with duodenal atresia, is exactly the same as taking a Down's baby off a respirator and letting the infant gasp and die, or injecting morphine into a newborn with multiple anomalies.

The usual argument parents bring to the surgeon is that God didn't want this baby to live—if God wanted this baby to live, he would've made the baby perfect, able to eat and to move his bowels. That the child has an intestinal obstruction means that God doesn't want it to live. It is very obvious, however, that God does create things that are imperfect and does endow them with life, just as he has endowed the healthy, beautiful, and lovely baby. In Judaic-Christian society, we accept the principle that every life is of infinite value, and that the value of every human being is absolute and not relative. For if it were relative, it would be relative to (a) life expectancy, (b) state of health, (c) intelligence, (d) financial resources of the family who will care for the patient, and—the most usual argument—(e) the baby's usefulness to society. But we really cannot divide people into groups having superior and inferior value, having a greater and a lesser claim to life. We cannot exempt the mentally retarded, the crippled, the unproductive, the undesirable individual from the guarantee of an inalienable right to life. Our society does not condone the destruction of a human life to relieve the suffering of another person (parents).

When any human being becomes fair game in the arena of the right to life, where does it stop? If physicians choose—as many medical centers have chosen—the Down's infant as a prime example of the patient who does not have the right to life so long as the parents agree to that judgment, what about the blind and the deaf? If the cripple in a wheelchair is the first target of such a choice, what about the retarded, the senile, the diabetic, the child with cystic fibrosis? If we physicians agree in principle that a Down's life is not worth saving, the day may come when part of our decision will be skin color, or religious convictions.

My approach to these complex problems is that if I make an error of judgment, I would rather err on the side of life. I would rather operate on a child with duodenal atresia who will grow up to be a retarded adult than withhold surgery from babies with lumbar myelomeningocele who could grow up to be young boys and girls who may need to use crutches the rest of their lives. A baby or a child is referred to me for my expertise in treating him or her, not for my expertise in neglect. When a patient is entrusted to my care, I will do my utmost to make sure that the patient is treated and cared for, not neglected.

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Rabbinic Comment: The Infant: Right to Privacy and Patient's Right to Know

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The right of privacy has been interpreted broadly to include areas of professional confidence. The lay person calls privacy a right and interprets it in a new light—the right to know everything that everyone else knows about his or her health care. For physicians to know something about the patient that the patient doesn't know is an invasion of privacy as interpreted by the courts in many cases these last few years. Therefore, all patients have a right to read their hospital charts. A patient has a right to know the basis of the credit rating given him by the credit bureaus. He even has the right to participate in medical decision-making. It is his right to reject or accept medical administrations or to be involved in deciding to use one modality of treatment over another.

The young neonate or pediatric patient or the incapacitated adult must, by necessity, extend the right of privacy to a guardian or a surrogate. This adds a new, more complex dimension to the analysis of the limits of this right. The cases presented so sensitively by Dr. Krasna concern, first and foremost, the question of humanhood. Does his deformity make him bereft of his most precious right, the right to life? What are the parameters of such anatomic or physiologic deformity? As Dr. Krasna so succinctly put it, where do you draw the line? Is there a difference between neonates whose rights to life are questioned and pediatric patients who have already established their right to humanhood by being born with Down's syndrome, but now present a newly acquired problem of kidney failure or accidental trauma that is also life-threatening?

Jewish Ethics. Biblical ethics are quite clear on the position of the neonate in the ethical stratification of Jewish society: "One life is not more important than another." A one-minute-old neonate has all the rights and privileges of an adult, tantamount even to the rights of the most important adult in the baby's life, the mother who gave life. Any decision concerning medical or surgical intervention for a neonate is guided by the same risk-benefit ratio analysis that applies to the adult patient. The prognosis of a life of intractable pain because of the need for multiple surgical procedures is cited by many as an ethical reason for nonintervention. In practice, however, it is almost impossible to evaluate the risk-benefit ratios involved. What do we mean by a life of intractable pain, a nonquality life? Do we really mean something the infant would not want to endure? Is it fair to judge a case on this basis?

There is, however, a law governing an extreme case of neonate deformity which I have to mention because it holds a strong position in biblical literature. The deformity is associated with prematurity and is recognized by our sages as a *ben chet,* "eight-month-old fetus," literally a fetus with eight months of gestational age behind it. But most commentaries commit a fundamental error in the interpretation of this law because the term does not really refer to eight months of gestation. *Ben chet* is an idiomatic expression, resembling the English term "a half-baked individual." Biblical literature identifies the *ben chet* syndrome only by three anomalies, three pathologies: (a) prematurity itself. If you know that the baby gestated for a full nine months, then all rights and privileges of an adult are automatically awarded to the infant. If the infant is known to

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be premature and has incomplete development of (b) nails and (c) hair, then our Jewish sages are willing to consider the baby as not entitled to all the rights and privileges of an adult. Whether any of the cases presented by Dr. Krasna can be compared to this syndrome is an issue that requires much more study. It requires much more ethical analysis than it can be given, because medical facts are missing.

Who Decides? The single most important issue in the right of privacy of the pediatric patient is the question of who decides. Clearly, in an emergency that demands immediate surgical intervention, only one person can decide—the medical professional. Too much time would elapse in any attempt to inform the family sufficiently to get not just consent, but informed consent, which is what is required. Physiological complexities in emergencies, plus the psychological trauma the parents are enduring, make it unlikely that parents contribute significantly to the decision-making process. The bioethecist has a specific role in such cases. Also, the legal community must provide some kind of good samaritan law that covers the physician in such situations.

A Cosurrogate? Traditionally, the family is the surrogate or guardian. This tradition must be questioned because, in practice, it may not be acceptable to assign decision-making to the family. First of all, the family is not always a friendly, unbiased surrogate. Second, family members do not always have the intelligence or the unanimity of opinion that allows the family to make an intelligent decision. Too often the private concerns of parents conflict with the rights of privacy of the infant. Considerations of financial expense and psychological stress on parents and siblings are often the dominant forces in this decision-making process, not the rights of the infant.

I would propose a legal requirement for a cosurrogate to review all family decisions concerning an infant to prevent violation of the child's rights by the family. For example, I recall a case of meningomyelocele with an excellent prognosis. The neurologic deficits were expected to be limited to the leg below the knee. The family was led by a prominent clergyman who argued for benign neglect. He fabricated data to support his recommendation. The sensitivity of the pediatrician who blew the whistle and the expert testimony of Dr. Krasna, who I called in on the case, contributed much. Leading religious and medical authorities insisted that the child be treated immediately. The family had even refused antibiotics. They removed the child to a private sanatorium, where the child died after nine weeks without treatment. Whose rights were being protected? How much quality of life was offered to this child during those nine weeks? How friendly is a mother who underwent an abortion in the twenty-fourth week of pregnancy and then gave birth to a viable fetus in need of massive intervention? How confident are we in the decision-making of this mother or in her friendliness as defender of the family and surrogate protecting the rights of this infant? Obviously, the accepted assignment of the role of surrogate to the family should be seriously questioned.

The role of intelligence in decision-making or in giving informed consent must also be addressed. Is the family competent to decide? If the right of privacy includes participation in decision-making, which includes deciding between treatment modalities, can the family grasp the manifold problems in managing the high-risk neonate in a sophisticated intensive care unit? Can they intelligently understand the potential for iatrogenic disease induced by the many life-saving measures that must be taken? Retrolental fibroplasia of the neonate is still a problem. Those infants need especially high concentration of oxygen. Bronchopulmonary dysplasia is still a complication of respiratory support measures. Who decides to keep a child alive at the cost of eyesight? Who amputates the legs of a neonate who develops saddle-block thrombosis as a result of the umbilical catheter that was put in as part of life-saving therapy?

I have personally been involved in just such cases, and I can't imagine a family making such decisions. Only a trained team of medically sophisticated ethicists, assisted by the family, can make such decisions.

Basis of Decision-Making

Substituted Judgment. The legal profession, which really speaks with the voice of society, basically offers two approaches to the question of surrogate decisions. The first is referred to as "substituted judgment." This is the key factor in managing the incompetent adult patient who has a track record of personal preferences, a philosophy of life, prior expressed wishes: you ask, What would the patient really want if he were competent to decide? The principle of substituted judgment is not relevant to infants.

How do bioethicists decide to advocate or not advocate operation for patients resembling those described by Dr. Krasna? How do bioethicists decide whether to advocate operating on a thalidomide baby who has duodenal atresia? By asking a nurse or a doctor or a sibling, Would you want to live with such a deformity? By reviewing the hundreds of cases of living young adults who have this deformity. By asking them in person if their life is meaningful. Do they seriously contemplate suicide? Would they rather be dead than alive?

Best Interest. A second basic approach to surrogate decision-making is referred to in legal literature as the "best interest" approach. It entails responsibility to promote the good of the patient and to decide in accord with acceptable standards. If more than one approach is acceptable, then any one of them is acceptable and may be chosen by the surrogate. The interests of society, the financial problems of the family, and triage issues of society are significant in the best-interest approach. Too many physicians base their decisions on the assumption of a "best interest" as they see it. The decision is not based on the substitutive role that a surrogate must assume.

Confidentiality. One other area, classically an area of patient rights, also affects the infant. The patient's right to privacy, the simple professional ethics of keeping things in confidence, becomes very complex when the patient is an infant, because as long as the infant is an infant, there is no problem—the parents are your patient and questions of confidence relate to the family, not the infant; but what happens when the infant matures?

In the famous XYY chromosomal study at Yale, it was in the best interests of society, the patient, and the patient's family to know how the child would develop, assuming the hypothesis that the chromosomal anomaly may lead to criminality. However, it proved not to be in the best interests of the child. The study was terminated when it was decided that the child's rights were being violated for the benefits of parents and society.

What about the adopted child and the search for his or her roots? The problem is not a child's simple curiosity about biological parents. What about genetic facts? Should the child be informed about the genetics of his biologic parents? Did the parents suffer from diabetes? Did the mother, grandmother, or two aunts die from breast cancer? Did the family suffer from familial polyposis of the colon, schizophrenia, or maybe even lung cancer, which may have a genetic basis? Is it the patient's right to know, or does the confidentiality that the physician owes the parents, both biologic and adoptive, take precedence over the rights of the patient—who is really the child, not the parents?

These issues have not been handled intelligently in the literature thus far. What is the social import of knowing whether a child was conceived by artificial insemination from a donor? What if hematology tests prove that the father cannot be the father? Does a physician tell the patient? Is it the patient's right to know? Under the present interpretation of the patient's right to know, a physician cannot know anything about the patient that the patient doesn't know. Do you tell a patient that he is a bastard? Can you tell a patient that he has no vas deferens or that she was born without a uterus? If yes, at what point do you tell? Which patient is entitled to these patient's rights?

These issues and many many more like them make up the daily bread-and-butter of a bioethicist. We need much help in making such decisions. A Torah portion describes the gestation of Jacob and Esau in the womb of Rebecca. The sages tell us a strange story. The mother wanted out. She was unhappy with the pregnancy. She thought she conceived a child that was somewhat mixed up. When she associated herself with things that were beautiful and ethical and moral, she sensed that the child was trying to push forward and get out to join the proceedings. At the same time, when she passed by areas of degradation, areas in which ethics and morals were not being practiced, she sensed the same desire of the child to get out, and she was so disturbed that she appealed to the prophets of the time for an explanation. When she was told that they were twins, she was contented. It was not one child, a schizophrenic child and a fence-sitter, but two children. The reaction of Rebecca was, "I can cope with anything that God throws at me. I can cope with that, but I cannot cope with indecision." I think this is true in the right to privacy too. We can cope with any problem, but we cannot cope with the problem of indecision. We must grapple with the difficult medical ethical dilemmas discussed here and reach decisions that will be pleasing to God and to human society.

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The Infant with Severe Anomalies: Should Life-Saving Surgery Be Performed?

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We physicians are frequently faced with deciding whether an infant with severe anomalies should be given life-saving surgery. Many factors affect our decision. A physician may favor one therapy over another. One physician may consider a condition to be not serious, a particular treatment for it not extraordinary, and reasonable. Another physician may view the same treatment as extraordinary, nonreasonable, and unusable. Is consent truly informed in that respect for the family's decision is maintained? What will be the outcome of surgery, and is it explained? Can a lay person really be fully informed on all the problems involved? What is the prognosis? "Prognosis" is a doctor's opinion, and is based on two or three factors—his own experience, if he has it; the experience he reads about; and possibly the experience he hopes to obtain.

A physician's opinion has many facets and is a combination of multiple points of view, formed out of his or her cultural background. Can there be only one ethic? Is this ethic to be followed in any given hospital for a patient? What happens if the physician is from India, from Africa, from the United States? If he or she has multiple cultural or religious backgrounds, what will his judgment be? Cultural background may affect judgment about what to do for a particular patient.

Does the physical appearance of the patient (ugly, "nice") mold the doctor's judgment about prospective quality of life for the patient? What organs of the patient are involved in functional deficits, and what are the doctor's own feelings or background about those organs? What does the loss of a leg or a baby born without a right arm mean to a physician, and how does he or she interpret about the long-term prognosis for the youngster, with or without other anomalies, to the family? Whether such a youngster should have a surgical procedure as a life-threatening emergency is, in fact, formulated through and within the doctor's philosophy. What does hospitalization mean to the family? Will the doctor project to the family the idea that they will visit the child, who may have meningomyelocele or Down's syndrome, every day in the first few days of life at the time of psychological bonding, and then, as the weeks go on, come once a week, then maybe once in two or three months? Parents may actually abandon the child until the child has to come home. The physician may decide that that is not a good enough quality of life.

A patient born without a right arm and mentally retarded needs abdominal surgery as well. Is this case different from the case of a four-year-old who is mentally retarded and lost an arm in an accident? Both have no right arm. Both are retarded and need surgical intervention. What are the conditions in the patient's family? What is the makeup of the family? How does the family condition influence the physician in relating to the parents and other family members? At the same time, what in the family's background will affect relationships with that particular child? What problems, real or not, does the physician project to the family? What about religious be-

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liefs? The religious beliefs of the doctor may differ greatly from the beliefs of the family. What are the differences, and how can they be coordinated in a way that results in a reasonable approach?

A discussion with parents is essential in ethical and moral decisions. Is there full disclosure of general conditions? Is the current condition of the patient always discussed with the family, and is it understood by the family?

Who should decide that an infant with multiple anomalies should not be treated for socioeconomic reasons? We know that such a newborn will be in the hospital for six months, which costs at least $54,000 in any hospital in New York City. So the question that was brought up by Dr. Morgenthau is absolutely reasonable. A young family starting out with a bill of $54,000 will have severe problems.

Last, but not least, what is the prospective length of life of the infant? Some diseases diagnosed on the first day of life will lead the doctor to one opinion. But if the same disease is diagnosed at three or four years when the patient has bonded with the family and has become an individual, the medical opinion may be different. Is a one-day-old patient an individual, and should he be treated similarly? An individual with juvenile diabetes may have a short lifespan, almost as short as that of a Down's syndrome child. Should surgery be withheld at 2, 3, 4, 5, or 8 years of age on the basis of the prognosis of a short length of life?

Euthanasia is often mentioned, particularly in pediatrics because of what is alleged to be a practice, putting babies with severe anomalies in the "back room" and passively allowing them to starve to death. Euthanasia is not so defined because of the pleasantness of the death, but by whether active or passive moves are made by a doctor. Decision-making is an active process. The doctor's mentation goes through every issue that he or she faces with a patient who needs a life-saving operation or procedure. Therefore, if he or she decides not to do something, he has actively, mentally done something. If he decides to do something, he is actively, mentally making that decision. So mentation is an active process. Applying Judaic ethics and morals to medicine is an active thinking process wherever the patient is concerned. The process involves many outside influences. These influences affect the doctor and therefore his or her approach to the patient.

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Rabbinic Comment: The Infant with Severe Anomalies: Should Life-Saving Surgery Be Performed?

RABBI LEONARD KRAVITZ

We Jews are a people of history; we have been almost everywhere and have experienced almost everything. Jewish history, therefore, is instructive as we confront new problems. Infanticide, however, is nothing new. It is as old and as widespread as birth itself. Our forefathers in Egypt faced the systematic use of it. The Torah records Pharaoh's command to his midwives, "When you deliver the Hebrew women, look at the birthstool, if it is a boy, kill him; if it is a girl, let her live" (Exod. 1:16). When they demurred, Pharaoh charged all his people, saying, "Every boy that is born, you shall throw into the Nile, but let every girl live" (Exod. 1:22). When our forefathers entered Canaan, the Torah warned them not to follow the practices of the Canaanites, particularly their penchant for infant sacrifices: "Do not allow any of your offspring to be offered to Moloch" (Lev. 18:21). Anyone who did so was to be put to death (Lev. 20:2). If the people did not attend to the matter, then God himself would (Lev. 5:6).

The Book of Jeremiah recorded the place where these horrid sacrifices took place and gave us another name for hell: "And they built the high places to Baal which were in the valley of ben Hinnom [*gey ben hinnom*] to pass over their sons and their daughters to Moloch" (Jer. 32:35). The late Dr. Nelson Glueck, president of Hebrew Union College–Jewish Institute of Religion and a noted biblical archeologist, once noted that if one excavated in Israel any settlement dating back to the second millenium, the time of Abraham, one invariably found baby bones beneath the lintels of every house.

To the world into which the Torah came, the story of God asking Abraham to sacrifice his son Isaac came as no surprise. What was surprising about the story was that God did not ask Abraham to follow through. Indeed, God forbade Abraham to kill his son.

The motivations of the pagans who worshipped Moloch and who offered up their infants were of the highest order. The sacrifices of babies were done to please their gods and to insure fertility within the family, within the flock, and within the herd. From their point of view, it was to preserve life that they took life.

However, as the Midrash reminds us in its discussion of the Cain and Abel story, the highest motivations may lead to the basest actions. One theory about the quarrel between Cain and Abel was that they argued about where the Temple would stand in the future. Abel wanted it in his area, Cain wanted it in his. In differing on where God would be worshipped, the one killed the other. The highest reason—the worship of God—led to the worst act, murder.

One can even make a case that, from Pharaoh's point of view, the slaying of the Hebrew children had high motives: the defense of Egypt against the hated Hebrews, who would otherwise link themselves to any potential enemy and rise up out of the land.

Among the Romans, who dominated the early rabbinic period, it was commonplace to expose children to the elements—those who were sickly or weak in appearance were taken out to a field and left there to die. Again, one could make the argument that this practice was followed for the sake of a strong Rome.

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It is in the context of the memory of what the Egyptians had done to the Israelite babies and what the Canaanites had done to their own infants and what the Romans were doing to their own children that we can fully appreciate the Mishnaic discussion:

> If a woman was in hard travail, the child must be cut up while it is in the womb and brought out member by member, since the life of the mother has priority over the life of the child, but if the greater part of it was already born, it may not be touched, since the claim of one life cannot override the claim of another life (Oholot 7:6).

Once the greater part of the child has emerged from the uterine canal it is a *nefesh,* a "life." It cannot be touched. It is even more sacrosanct when the infant is out completely and is born alive. At that moment, it has a claim to life equivalent to everyone else's.

Noone would raise a question about the claim to "life" of what might be called a normal child. Where questions arise is in the case of a birth anomaly, when there is something wrong with the child. Jewish law, however, sees the life of each infant as having value in and of itself. Jewish sources certainly knew birth anomalies: of sexual differentiation, the *tumtum* and the *andrygonus*—those of doubtful sex or those having the outer genitalia of both sexes; of physical appearance, facial and bodily, which according to the Mishnah in Bechorot, chapter 7, disqualified those of priestly family from serving as priests; and those of mental incapacity, the *shoteh,* whose disabilities fill pages of rabbinic discussions. All of these unfortunates were available to be discussed in their various legal contexts because there was no attempt to eliminate them at birth. Once they were born alive, they were maintained in life. To save their lives, the sabbath and other holy days might be profaned.

The Talmud discusses a severely malformed infant having a double back and a double spine. It is not clear, though, from the language of text (*ha-mapelet briyah,* in T. B. Bechorot 43b) whether what is being discussed is a live birth or a miscarriage. However, *Sefer Hasidim,* a twelfth-century or thirteenth-century work, records—and modern discussions (Rosner, in M. M. Kellner's *Contemporary Jewish Ethics,* page 265; and Jakobovitz, in *Jewish Law Faces Modern Problems,* page 75) quote—the case of a child born alive with teeth and a tail. Should such a child be killed? was the question put. The answer was No. What was advised was the removal of the teeth and the tail.

An 1807 responsum of Rabbi Eleazer Fleckles of Prague (quoted by Jakobovitz in *Jewish Law Faces Modern Problems,* page 45) deals with a monster birth. On the basis of the talmudic passage which excluded the mother of the baby born with the double back and the double spine from certain ritual laws of impurity, Rabbi Fleckles was asked if a monster child might be killed as somehow not being human. He replied that once the child had been born alive, however deformed, it could not be killed, an act of commission. Nor could it be starved to death by not feeding it, an act of omission. Either act would be unlawful as homicide. (The same reasoning has been used by Rabbi Jakobovitz in his tragic chapter on the thalidomide babies.)

The prohibition against allowing a child to starve to death is instructive in considering methods of dealing with severely deformed children. It is wise to remember that no child, "normal" or otherwise, can live without being fed. Not to feed a child is to kill a child as surely as putting a pistol to its head and pressing the trigger or injecting strychnine into its heart.

Rabbi David Bleich, in M. M. Kellner's *Contemporary Jewish Ethics* (page 301), has noted the parallel Maimonides draws between food and medicine. As God has created the one to deal with hunger, he has created the other to deal with illness. As we are bound to use the one, so are we bound to use the other. It would follow, then, that as we may not withhold the one, for that would be homicide, so we may not withhold the other, for that too is homicide.

Withholding treatment cannot be described as "doing nothing." When the ancient Romans "exposed" a child, they were doing something; they were letting that child die. They knew what they were doing. Placing a child in a field was an act, an act which entailed the death of that child. Placing a child in a back ward is an act, a conscious act, which equally entails the death of that child.

It could be said that the child will die anyhow at a later time. I am reminded here of the Midrash in the passage of the Torah (Gen. 21) which we read on Rosh Hashanah and read again during the sabbath cycle. Hagar and Ishmael are lost in the wilderness. Their water is gone. They face imminent death by thirst. In her anguish, Hagar has cast away her son that she not see him die. At this point, God is about to show Hagar a well of water that she may save herself and her son. The angels object: Ishmael will grow up to be wicked, he will become an enemy of the Jewish people. Let him die! God asks them: What is he now, innocent or guilty? They answer, Now he is innocent. God responds, *baasher hu sham,* "as he is now, he deserves the water." The midrashic principle can be extended. Can this baby be saved now, can his or her life be extended? Unlike the angels, we don't know the future. Let us extend the child's life.

Life in Judaism is a divine gift. Every baby has three partners, said the rabbis, in his or her creation—father, mother, and God. Every physician who is given the divine license to practice in the words *rapoh yirapeh* (Exod. 21:19) has the obligation to support the divine quality of life.

This is not to say that there are no questions and that there is no anguish in making such decisions for life. Moral decision-making is rarely involved with good against evil, which is easy, but rather with good against better, and bad against worse. The decision for death even for the "best of reasons," even for the "quality of life," has its own entailments. As Jews, we should remember that the move toward the extermination of Jews in Nazi Germany began with "mercy" killings. Once you start killing defectives, mental or physical, it is a small move to the defining of a specific group as defectives—and the locomotive on the track to Auschwitz begins to roll.

What will the criteria for the trip to the "back ward" be? Physical appearance? Function? Life expectancy? A decision to terminate a life is indeed a "final solution."

The prophet Micah, faced with the conventional wisdom of his time, with the idea of child sacrifice, of infanticide, as a way of expiating sin, of getting closer to the deity, said, "Shall I give my first born for my sin, / The fruit of my body for the sin of my soul?" (Micah 6:7b). His answer to the question was an implicit No. He then continued in the words we know so well, "He hath told thee, O man, what is good / and what the Lord asks of thee, / Only to do justly, to love mercy, / and to walk humbly with thy God" (Micah 6:8).

Micah's words suggest that in decisions relating to infants with anomalies, we follow the lead of Jewish law, that we may do justly; that we be sensitive to the anguish of such decisions, that we may love mercy; and that in all we do, we attempt to walk humbly with our God, the God of life.

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Beginning of Life: Discussion

Moderator: Donald Gribetz, M.D. Discussants: Rabbi David M. Feldman, Rabbi Macy A. Gordon, Kurt Hirschhorn, M.D., Irwin Krasna, M.D., Rabbi Leonard Kravitz, Joseph J. Rovinsky, M.D. and Rabbi Moshe D. Tendler, Ph.D.

Questions were posed by members of the audience and were read by the moderator.

Question: Rabbi Tendler, what information does the rabbi or ethicist require from the physician to answer rabbinic questions of medical ethics?

Physician–Rabbi Exchanges

Tendler: The most serious question is, What information can the rabbi absorb from the physician? One of the big practical problems in medical ethics, at least in Halachic ethics from the Torah point of view, has been to find the dual expertise necessary to make intelligent decisions. Discussions like those of our Ethics Committee are essential. Dr. Greifer suggested an approach from the medical point of view. But these are not two points of view. We are not speaking of a doctor and an ethicist. We are speaking of an ethical physician. An ethical physician requires an ethicist who understands the medicine; the ethicist requires a physician who is sensitive to the ethical issues. The answer to the question is that every bit of information is critical in making a decision. The medical factors, physiological, biochemical and, of course, sociological and familial, the lifestyle of the patient, and the wishes of the patient all play into the making of a decision. The delay in coming to decisions on specific cases is simply the end result of our inadequacy; answers are available to those who would search for them.

Genetic Engineering

Question: What about substituting healthy genetic material for harmful ones in the babies during in vivo conditions?

Hirschhorn: Actually, that question is not as farfetched as it would have been five years ago, when it was purely science fiction. It no longer is. We are always surprised at how long it takes for simple problems to get solved and how quickly complex problems get approached via technology. Before too long, it will be possible to transport genetic material into cells. It is already being done in the test tube. It is being done certainly with bacteria. It is being done with tissue culture cells, whose basic genetic defect has been corrected by introducing genetic material to the cell to make up for the missing enzyme.

There are other approaches to what some people call genetic engineering—more accurately, biological engineering—via prenatal therapy for certain diseases. In particular inborn errors, high doses of some vitamins may overcome a defect and give the baby a better chance when it is born, so the general question of a therapeutic approach is going to become reality.

The basic question must be asked again from the point of view of resources. As it stands right now, technology that is potentially involved in such solutions is enormously difficult, and enormously expensive in resources and personnel. The social question will come up as the whole field of therapy of genetic diseases blossoms. In at least 14 diseases, dietary therapy can now make a previously abnormal child normal. We are looking at enzyme replacement therapy for a variety of diseases. There is in prospect—though not yet fact—a reasonable chance of success in treating Gaucher's disease with enzyme replacement therapy. At this stage of our knowledge, however, we cannot treat Tay-Sachs disease the same way because of the blood-brain barrier, which nobody seems to be able to get around. Yet, the possibility is going to be there. It will depend on the advances in technology and on the cost of that technology. But there will be an ethical problem of equal access. Until very recently, even in our own institution, 95% of amniocenteses were done for the private sector. It took an enormous amount of effort and persuasion on our part to make this advance in technology available for the clinic population.

Tendler: It is not possible to look only at the potential dangers of a medical advance; the potential benefits must be carefully evaluated. The risk-benefit ratio, the chance of curing genetic disease, is indeed a key factor. We have a lot of confidence in American ingenuity. The possibility of making genetic corrections for sickle-cell anemia or for Tay-Sachs is always there. In our world view, we're not prepared to close any door to investigations on humans. All we ask is that there be a keeper at the door that determines who goes in and what comes out.

Parental Decisions

Question: Dr. Krasna, if your decision to operate is in conflict with the choice of parents, who refuse because the newborn's life span is short, first, does the counselor consider and understand the pain and emotional investment in a baby who will die shortly? And second, is the parents' desire to protect themselves against the pain just as much an ethical issue?

Krasna: Life isn't gentle. Whan a baby is born with Down's syndrome, even if the baby does not have intestinal problems, the parents' future is very difficult. Naively, physicians and most pediatric surgeons have taken this issue in hand. For example, the pediatric surgical group at Johns Hopkins has produced a movie making a case against operations on Down's infants with biliary atresia. The movie shows how a baby was put in a back room without intravenous assistance until it died. This is an honest statement. There is no difference between not doing something essential and doing something actively. If you are not taking care of the essential needs of a patient, that is identical to doing something to hasten death. Even if you have given birth to a baby, even though you are the baby's parent, that baby has a life of its own. When I operate on one of these Down's children, I always tell the parents I will do everything I can do, together with the social worker, to place the baby patient in an institution. If they don't want to take the baby home, their decision is understandable. But why should the decision fall upon the pediatric surgeon? Most importantly, why should the pediatric surgeon make this decision not to operate upon the baby? Certainly, if the patient is an older child with Down's syndrome, or a child with leukemia and appendicitis, no surgeon would refuse to operate. It is a dilemma. Any choice you make is an unhappy choice. But nobody has the right to sacrifice one person's life to make another person's life a little bit easier.

Tendler: The issue raised is the most heartrending of all. A parent, especially one who is socially active, has friends who have children with Down's syndrome. They know of children who die of Tay-Sachs. The fear and the concern that the parent expresses is well understood. We bump into a strictly legal consideration. There are some people that I don't like. If I thought of ridding myself of my dislike or my discomfort by taking their lives, I would be a murderer. The issue is a very simple one. The pain that the parents must endure has nothing to do with the child. Once the child has breathed the air independently, the parents' concerns are secondary. This is the stance upon which the moral fiber of our society depends.

Yet the Judaic law is clear: You cannot kill the child to save the mother. This is what I meant; we can't substitute one life for another. As long as the fetus is still totally dependent upon the mother, other rules apply. Jews are prepared to sacrifice fetal life only for adult maternal life. The idea of extending fetal life into the first, or second, or third year of life and say that a child with three years of life is still fetal, so that maternal concerns come first, is a violation of fundamental secular ethics and biblical ethics.

Krasna: I might add one perspective on what parents are feeling at the time they are contemplating such a decision about an infant. We tend to respond to parental distress very quickly. But we must recall that one of the things that might be occurring is that the parents are mourning what might have been. The child they had hoped for is not there. In the midst of this, they have to make a very difficult decision. We could give them a few days, and allow them to experience that mourning before a decision has to be made.

Differences between Fetus and Infant

Question: Can you describe any morally relevant differences between the clearly viable infant at 30 weeks and the newborn baby?

Feldman: The answer is the differences are indeed moral, not physical.

It is a metaphysical determination that gives human life status to the fetus before birth. You may say that independent viability is the factor. Since the fetus is still dependent upon its mother, it is not an independent human being. But then that raises problems too. Dr. Edles in Boston, after performing an abortion, found that the fetus was still alive outside the womb; he allowed it to die but it was not then dependent on its mother. The only distinction has to be based on a metaphysical determination pivoting on the cut-off point. Otherwise, why any point in the spectrum? why 30 days, or 30 weeks? All life is precious and has to be protected. The sabbath and Yom Kippur can be violated to preserve life. But there must be a cut-off point when a fetus competes equally with the life of the mother, and the life of other humans when murder, in the absolute, applies.

Tendler: There is one legal difference between fetus and infant. We play the numbers game in law too. A child that has been born has already survived the additional risk of the birth passage. Active murder is punishable by law. There is a difference between a person who has a sure claim on life (the infant) and someone who has a questionable claim on life. Therefore, there is that distinction. Someone who kills a fetus once it's born is open to a capital charge of murder, whereas someone who kills a fetus is not necessarily, even though at 30 weeks the fetus is fully viable—it can be born and live independently. The distinction is there, but this is a legalistic distinction which has to do with the problem of humans punishing each other, not the certitude of God punishing man.

Hirschhorn: This really goes many steps beyond what the two rabbis are addressing. You're talking about an act of murder. But what does the act mean? Just turning off a machine, is that an act of murder? The data collected from our own Intensive Care Nursery, which has excellent survival results, and where I make rounds once a week, tells us two things. So far, very few babies under 700 gm have survived, despite all the efforts in our nursery. Also, if we look at the follow-up data, babies between 700 and 1000 gm present problems of long-range quality. Therefore, where does the decision on how hard you try come in? How long do you try? What do you have to look at, or do you get bogged down—as many neonatologists do—in the effort itself, and forget about all other consequences? How hard do you work on a 600-gm infant when you know from your past experience that you haven't learned anything new in technology and that all the other babies at that weight have died? How much are you expending in terms of energy that might be used to help some other children? This question goes byond the question of the rights of the 30-week versus the 25-week fetus in utero versus the newborn, to the question of rights after birth.

Withholding Treatment

Question: Rabbi Kravitz, you mentioned that not treating a child is the same as killing the child. Do you think the same opinion applies to an adult who has fatal cancer and develops pneumonia? Do you feel that denying this patient treatment is tantamount to killing the patient?

Kravitz: It is the same category of process. What you are after is, What is the intent? Very often in our own minds, we don't want to say we, in fact, killed the patient. So we say we treated as far as we could. A distinction between an extraordinary and an ordinary measure is no longer possible. What was extraordinary yesterday is today ordinary. By tomorrow it will be commonplace; and the day after that, it will probably be superseded.

We are batting with a sticky wicket if in fact we intend to keep the patient alive by all the methods we talked about. The intention in not treating a patient is equivalent to asking the patient to die. The difference between a baby and an adult is that we are sure in the case of a baby. The question might be, if the person is in the throes of death, and if we simply cut off oxygen, that ends it—we didn't do anything, but we would be held accountable. These things are equivalents and part of our problem, again, is not facing what we really intend.

Question: What is the ethical position of the physician when the parents refuse surgery for the defective newborn? If by chance the courts uphold the parents' decision, does the physician refuse to continue care of the baby?

Krasna: This arises many times. Usually, I tell the parents that if they refuse surgery, they should take the baby out of the hospital, out of my care. I have never had a parent who agreed to take the child home to put the child in a crib and let the child vomit until it dies. They will never take the responsibility. They always want the physician to take that responsibility. I would generally sign off a case like that. Certainly, I cannot be responsible for how babies are treated in any other hospitals that I am not familiar with. At The Mount Sinai Hospital in New York, whenever we have had this situation, we have a court order issued. We operate on these children. It is conceivable that a court order may say not to operate on the child. The only legal responsibility this doctor could take then is not to be the physician. Historically, at least in this hospital, there has never been a court order telling us not to treat. We have gotten court orders, rightly or wrongly, but we have gotten court orders always to treat.

Abortion

Rovinsky: Dr. Tendler, please rationalize one of the statements that I made initially. Namely, it is ten times safer for a woman to have an early abortion than to have a normal pregnancy. What of the woman who requests an abortion because she doesn't want the risk of pregnancy?

Tendler: This is an example of a certain psychological set, a world view. Life is a terminal illness. The risks of living are what we call life. If you believe that we are social beings and that any one of us alone is unfulfilled, then part of our fulfillment is to establish a family. This continuing fulfillment is for the family to establish societies. This is the man that God put on earth. This is what we mean by "man was created in God's image."

It is frivolous to equate the dangers of pregnancy with the dangers of abortion. It is like equating the dangers of being alive with the dangers of being dead. The risks that a person takes to stay alive are the proper risks. There are risks in fasting on Yom Kippur for someone with incipient cardiac problems. Yet those who believe in our tradition accept this risk because this is the way the Jew lives. You are equating the way the Jew lives with the way the Jew kills. That is not a fair equation. Also, I would like to correct a mistaken notion presented earlier when the Talmud was quoted—the statement "a fetus less than 40 days old is like water." This statement is misunderstood by many and is, therefore, misquoted by almost everyone. The definition of a humanoid form, or human being, varies in theological or legal sense. A Kohain cannot defile himself by contact with the dead. If a fetus is less than 40 days old, it does not defile a priest. "Forty days old" is a factor in determining whether burial is needed. It is not required that the laws of mourning be observed for stillbirth which has existed nine months in gestation, even though it is clearly a human being. The term "40 days old" must be understood in the light of what I said earlier. We are prepared to violate the Sabbath, to desecrate Yom Kippur to save the life of a fetus less than 40 days old. We are willing to suspend all our ritual laws; so, obviously, the fetus is not "like water."

Question: Abortion may indeed be murder, but may be committed for extreme internal factors under the laws of *rodef* ("pursuer")—if a person is in pursuit of another, the pursuer can be killed to protect the victim. It is a very interesting concept suggested in the Talmud which proposes that a fetus can be aborted if it constitutes a threat to the mother. So even though Jewish law says that murder is never allowable, that law does include this concept of justifiable homicide. One ought to be able to abort under that law.

Feldman: Maimonides says that if a woman is in difficult childbirth, the fetus can be dismembered to save the mother under the law of *rodef,* although the Talmud prefers other reasons to permit that. My book *Marital Relations, Birth Control and Abortion in Jewish Law* (Shocken Books, 1974) devotes several pages to *rodef* as a particular resolution of the problem of abortion. Jewish law is not so flexible on abortion. Perhaps the most extreme Jewish anti-abortion point of view is that of the late Rabbi Isar Unterman, chief rabbi of Israel. He wanted to say that abortion is murder but, bound by legal tradition which does not say it, he could not. Instead, he said that abortion is like murder; it smacks of murder; it sounds like murder. It is all these things; therefore, don't do it. Unterman appropriately brought in, as Rabbi Tendler did, Cain and Abel. When Cain killed Abel, the Torah says God said to Cain, "Where is your brother?" Abel replied, "I don't know. Am I my brother's keeper?" God said to Cain, "What do you mean, you don't know? The sounds of your brother's bloods [plural] are crying out to me." Why "bloods" in the plural? Because when Cain killed Abel he killed not just Abel, but all Abel's possible children, grandchildren, and greatgrandchildren. So how serious is it to have an abortion, if abortion kills all the potential offspring? Yet we are not going to accuse Cain of mass murder. We have to be technical, we have to be strict in our legal categories. He wasn't legally guilty of mass murder even though, metaphorically, he was, because Abel was a young man still capable of fathering children, from which he is now deprived. Rabbi Unterman says all this and then relates the following incident:

During World War I, a German soldier impregnated a Jewish girl. The soldier insisted that the girl get an abortion. The soldier took her to a Jewish doctor for the abortion. The doctor refused for religious reasons. The German soldier pulled a gun and threatened to kill the doctor if he wouldn't abort the girl. Rabbi Unterman said, "If I were in that scene and were asked whether I should perform the abortion or allow myself to be shot, I would have to say I should perform the abortion. The doctor should not allow himself to be shot because the abortion he would perform is technically not a murder. If it were, then he would have to allow himself to be shot rather than commit murder. Since it is not murder, this physician cannot martyr himself. He should abort the girl and save his life."

Question: What about a woman who aborts herself, whose husband wants to divorce her against her will. In Jewish law a husband must have good grounds to divorce a woman against her will. Can he divorce her?

Feldman: The answer is no. If she committed murder the husband could divorce her. She committed an abortion; that is not murder, therefore, she cannot be divorced against her will. Ridbaz has an interesting responsum concerning a Kohain (priest) who struck a pregnant woman and caused her to abort. Is he guilty of murder? A Kohain cannot bless his congregation if he is guilty of murder. Ridbaz says no, not in the technical sense, the Kohain who committed abortion is not guilty of murder; he can come to synagogue and recite the priestly benediction.

Gordon: The Torah tells us of a revelation during the Exodus. A man caused a pregnant woman to abort during a fight. The man was forced to pay indemnity to the woman's husband, because he caused a monetary loss, not a capital loss. According to the Talmud and post-Talmudic literature, the Exodus revelation given to the Jews supersedes the Noahite laws (dating from the time of Noah). From the standpoint of Jewish law, abortion up to the moment of birth is not the taking of human life, it is the taking of potential human life. In a sense, this tradition was a political statement against the Roman rulers. When a weak baby was born, the Romans had a simple solution: put the baby on the rocks of the cliff and expose it until it dies. This infanticide so outraged the rabbis of the Talmud that they reinterpreted the verse. This is the distinction that the Ridbaz offers.

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II. Adolescence to Adulthood

The Rights of Adolescents in a Medical Setting

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Only in recent centuries have children been recognized as inherently different from adults and represented as such both in art and in the expectations of adults (1). The relative neglect of the special needs of children and adolescents in Western society persisted until the past few decades, a neglect clearly indicated by the instructions and laws adults imposed upon youth. That these instructions were sometimes ill-fitting, poorly attuned to youthful needs, and arbitrary has long been recognized. The peace and prosperity of this country following World War II, together with the better education of the young, led to young people's increasing independence and participation in decisions, and at the same time produced vulnerability to a new set of problems. While many adolescents have sufficiently mature judgment to make independent decisions, other teenagers have not yet achieved the broad and reliable perspective which facilitates such decisions.

Sexual Freedom and Individual Rights: Contraception and Abortion in Adolescence

The availability of contraception and abortion to adolescents has poignantly focused these trends. The possibility of pregnancy, the threat of disease, the prohibitions of religion, and the shame-inducing practices of society had long maintained a clear, if permeable, boundary for sexual activity in adolescence. The development of treatment methods for diseases associated with sexual contact and of successful contraceptive techniques gradually opened to our view the sometimes arbitrary and irrational bases for proscribing adolescent sexual activity. Parents are now much less likely to restrain adolescent sexual activity by describing it as immoral, sinful, or a source of social stigma. In part, this has been the result of protest and negotiation initiated by adolescents themselves. To quote Shakespeare in *The Merchant of Venice,* "Why should a man, whose blood is warm within, / Sit like his grandsire cut in alabaster?"

The natural place of sexuality in an adolescent's life is now appreciated. Adults help young people cope with the obviously disruptive concomitants of sexuality by joining in arrangements for contraception and counseling in relation to sexually transmitted disease. Lost, in part, during this transitional period has been a recognition of the vacuum this leaves in the venerable relationship of adults to adolescents. Adolescents have traditionally rationalized any misgivings about engaging in sexual activity by explaining that parental restriction causes the sexual reluctance. In the view of adults, this explanation provides the adolescent a period of grace in which the young person's unique developmental processes can proceed at their own pace and in accord with individual preferences. Of course, the young do not necessarily take this view of matters and continue to protest such restrictions. There is tension and acrimony when advice is offered by adults. In this country we have recently inclined to the view that the intensity and confidence with which adolescents present their observations indicate the inherent righteousness of their point of view. Some of our ancestors have been less sure of this:

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The young think they know everything and are confident in their assertions. (Aristotle: *Rhetoric* II, xii)

Rashness attends youth, as prudence does old age. (Cicero: *De senectute*)

Young men are apt to think themselves wise enough, as drunken men are apt to think themselves sober enough. (Lord Chesterfield: *Letters to His Son,* January 14, 1753)

It is very natural for young men to be vehement, acrimonious and severe. (Samuel Johnson: *The Rambler,* No. 121)

It is the adults—usually the parents—who stand ready to give more evenly divided attention to the lives of the younger generation, stepping in with counsel when something critical has been overlooked. Whether it is truly critical or not is the source of never-ending generational conflict. At their best, adults are patient and tolerant with adolescents; to quote Logan Pearsall Smith, "Don't laugh at your youth for his affectations; he is only trying on one face after another till he finds his own."

This implies that the adult recognizes youth as a time for trial behavior and that these imitations and experimentations are critical to development. But they cease to be experimental when the adolescent is unable to extract himself from a role into which he has flung himself with such enthusiasm. This points to one of the advantages of access to a friendly adult who can help the adolescent subdue some of the excesses to which this period is given, allowing the young person the chance to try out yet other parts in the drama. Too often in recent years, adults have been confused about their roles and have never taken a part. Thus a vacuum is created, and the adolescent may well cast about elsewhere seeking to fill it. This process often leads the adolescent to a physician for consultation. We physicians find ourselves searching not only for answers dependent upon our professional training, but verging perilously on the limits of the parental domain. We know full well the adolescent is both seeking advice and likely to reject it. What are some of the guidelines that our knowledge of developmental processes might supply to aid us in formulating a response?

If we as physicians can assume that the hard-won liberalization of attitudes toward adolescent independence will be sustained—and this is a vulnerable assumption, given the swing of sociopolitical opinion—then we can concentrate our attention on understanding the basis for an adult's intervention and guidance.

Consider the adolescent requesting contraceptive advice. She might well insist upon our arranging for her contraceptive measures without her parents' knowledge. She is convincing in her description of the genuine risk of pregnancy were she not to use a contraceptive. Her ardent defense of her right to decide these matters for herself strikes a responsive chord as we consider our experience as physicians with teenage pregnancy in the past. She skillfully weaves into her plea some of the more irrational comments which her parents have made on this topic. Yet we feel a growing awkwardness as we contemplate whether our response will in any sense involve an unwarranted assumption of a parental posture on our part. Knowing the intense, sometimes ill-chosen response of her parents, we sympathize with her right to privacy. At the same time, we feel she has a right to know about these matters, a knowledge communicated by someone relatively free of biases or emotional involvement in this circumstance.

It is here that physicians encounter some confusion. The right to know can cut both ways. We must consider to what degree she is capable of knowing. Ten years later, she may bitterly recall that no one defended her against her own immaturity, no one cared enough to recognize that she was not yet capable of understanding the ramifications of her behavior. Someone should have been there to protect her right to develop until she could truly know the meaning of her actions.

It is in this context that I turn to examine five sectors of the adolescent girl's development which guide my response: the effects of rapidly changing levels of compounds active in the central nervous system, altered cognitive capacities, movement along the developmental line of responsibility for the care of one's own body, progress in psychosexual development, and the current status of the enduring struggle between the wish for dependence and the need for independence.

Developmental Perspectives on the Rights of Adolescents

Effects of Puberty on Brain Functions: Shifts in Hormone and Neurotransmitter Levels

Few adults can vividly recall the experience of the rapidly changing size of the body during early adolescence: the sudden sense of awkwardness; the chagrin at no longer looking like the person one used to be, and not yet being the person one will be; the exciting but sometimes alarming awareness of a new sexual capacity; the knowledge that increasing muscle mass has suddenly given a new meaning to aggressive outbursts.

What the adult is even less likely to appreciate is that changes in the interior of the adolescent body are every bit as dramatic as those on the exterior. The levels of hormones bathing the brain are radically altered, an occurrence which can be postulated to be related to the rapidly shifting moods characteristic of adolescence. At the same time, the levels of a range of substances related to neurotransmitter function change during adolescence.

Although physicians usually emphasize the adaptive nature of new cognitive capacities to which these changes in brain chemistry contribute, the short-term effects of the changes may be disruptive. Since the developmental curves characteristic of each neurochemical substance are likely to be dissimilar, there is a shifting balance among them, contributing to the typical cognitive and emotional volatility of adolescence. Sexual, aggressive, and cognitive experiences during puberty are not only novel but may also be unstable because of this ongoing disturbance in the regulation of brain function. Psychiatrists have long been aware that adolescence is ushered in by a range of regressive behaviors representing a return to old and more familiar psychological defenses. It seems reasonable to postulate a relationship between changes in brain function and the altered behavior of early adolescence (2).

It is important for physicians to be aware that an adolescent who comes to a physician for advice about contraception may be vulnerable to such shifts in brain function. For example, the levels of urinary luteinizing hormone (LH) appear to increase approximately tenfold during adolescence (3). Such changes can occur in some individuals as late as the seventeenth and eighteenth years. Ignoring such bodily changes in the adolescent may lead to a counselor giving more responsibility to an adolescent than he or she is prepared for. F. Scott Fitzgerald caught the spirit of these thoughts when he observed that "everybody's youth is a dream, a form of chemical madness."

Cognitive Development And the Right to Know

To estimate the general range of cognitive capacities available to the adolescent, recall that Piaget has described an invariant sequential scheme of four stages for cognitive development. They are based on his own observations and experiments, which have been repeated by legions of students since his first reports. The first stage is entitled "sensory-motor," and characterizes infancy, or the first two years of life. The second stage is identified as "preoperational" thinking and indicates the cognitive style of early childhood (ages 2 to 6 years). The third stage is the "concrete-operational" stage of thinking, typically seen in middle childhood, ages 7 to 11 years. Finally, the fourth stage of cognitive development may be reached during adolescence and is known as "formal-operational" thought, often popularly identified as abstract reasoning (4, 5).

Perhaps the easiest, most direct method for characterizing this cognitive growth is to draw contrasts among the latter three thinking styles along several cognitive dimensions. Thus, the four-year-old preoperational thinker will typically be bound by the appearance of things. In contrast, the ten-year-old concrete-operational thinker moves ahead to assess the reality, which may or may not coincide with the perceived appearance. The four-year-old centers attention on a single feature of a stimulus, unconcerned that other features are neglected. The ten-year-old is capable of a more balanced consideration of a range of features, mentally decentering from any single point of special attraction. The four-year-old preoperational thinker is largely limited to the present state of an object, whereas the ten-year-old concrete-operational thinker appreciates transformations in the state of an object. Similarly, irreversibility is characteristic of early childhood thinking, while by middle childhood reversibility is typical. "Reversibility" connotes an understanding that an alteration in one feature, such as width, may exactly compensate for a change in another, such as height, in relation to a certain quality, such as volume. Overall, by middle childhood, our thinker has a decidedly more quantitative perspective and is more likely to use measurement as a tool. The child has moved to the point of appreciating the concept of an intellectual problem and a solution (4, 6).

The first point to be made about adolescence is that not everyone achieves formal-operational cognition. Adolescence brings with it the potential for abstract thought, but by no means demands it. A corollary to this is that an individual may achieve formal-operational thinking, yet use it irregularly or even infrequently. Obviously, both environment and motivation are critical factors here.

The ten-year-old, concrete-operational thinker approaches a problem by examining the data that are available, making a personal determination of "reality"; the thinker has advanced from a reliance upon appearances. The adolescent formal-operational thinker, however, begins problem assessment by imagining various possibilities, that is, potential realities. This leads to a sequence of experimental steps by which the abstract thinker attempts to determine which of these possibilities is actually "real" or "true." This, of course, is the stuff of scientific reasoning. Our thinker develops hypotheses and then deduces the empirical occurrences predicted by these hypotheses, only then verifying their reality in the real world. This cognitive activity is designated as "hypothetico-deductive," in contrast to the "empirico-inductive" thinking of the ten-year-old.

The ten-year-old's thinking is also characterized by the formulation of isolated propositions about reality. The adolescent abstract thinker, on the other hand, is interested in examining the logical relations between two or more propositions: a given proposition may imply another, while being contradicted by a third. Put briefly, the ten-year-old uses "intrapropositional" thinking, while the abstract thinker adds "interpropositional" thinking to the repertoire. The concept of interpropositional thinking is fundamental to the idea that the adolescent has a capacity for thinking that is completely abstract, totally formal-logical; anchoring points in the external, "real" world are not necessary. This type of reasoning, applied systematically, is capable of generating all possible combinations and permutations of a set of factors. The information processing strategies available to the abstract thinker are enriched and increased accordingly. We shall underscore these aspects of formal-operational thinking in the context of our discussion (4, 6).

How will this review of the formal nature of thinking aid us as physicians in our attempts to sort out what is best for our teenage patient in terms of her right to privacy and right to know?

An understanding of the development of thinking alerts us to the idea that an adolescent may not have developed formal-operational thinking, or may not use it much of the time, especially when confused by stress. This implies that she is likely to consider her current problem relatively exclusively in terms of its immediate characteristics. For example, it is more likely that the concrete-operational thinker will consider contraception in relation to only one or a few factors—perhaps including an intense need to initiate sexual activities because of a desire to escape peer pressure, or a fear that she might lose her boyfriend.

Recognition of possible medical side effects of a contraceptive and awareness of the actual commitment to an active sexual life implied by continuous contraceptive usage may be lacking. Even an intelligent adolescent of sixteen who preferentially utilizes abstract thinking may have difficulty comprehending the wide-ranging ramifications of her decision to initiate continuous contraception. Is she prepared for the intense, peremptory emotion of sexual intimacy? Or will the intense emotions drive her toward dissociation of her feelings and the establishment of superficial relationships? Has she weighed her own capacity to absórb the pain encountered at the loss of a loved sexual partner? Has she considered her ability to sustain her other personal objectives, such as her education, while involved in what may be the particularly volatile and disruptive emotional experiences of sexual intimacy? Has she moved far enough along in her separation from her parents that she can experience this new intimacy without a confused exaggeration of already disturbing emotions in relation to her parents?

Another familiar example is the teenager who seeks pregnancy, consciously or unconsciously. In this instance, the concrete-operational thinker may decide to engage in sexual relations only because she yearns to be held, wants to experience sexual pleasure, and would like to have a baby. The use of a contraceptive may be only a screen for this desire for a baby. Contraceptive failures will lead to the realization of the wish. An appreciation of a baby's needs or of the demands of parenting may be entirely lacking.

A teenage boy may only distantly understand his role in a possible pregnancy and his responsibility to a potential child. Here we contemplate the creation of a new, vulnerable human life by a child-parent whose thinking cannot encompass the future infant's needs. The child-parent will later feel cheated and tormented by the infant's demands. Can we physicians avoid asking where are the parents or friends—those people with a sufficient capacity for the abstract thinking necessary to consider these possibilities—of this child-mother or child-father?

The adolescent has a right to know not only that she has access to contraception or abortion, but also what medical facts are associated with contraception and with abortion; she also has the right to privacy as a patient. Finally, the adolescent has the right to know that she can anticipate that a parent will help her thoughtfully consider all sides of a situation when her own development does not make it possible for her to accomplish this on her own.

Responsibility in Body Management

Anna Freud formulated the concept of "developmental lines," a concept that may have greater practical benefit to the parent or teacher than the emphasis on symptoms so familiar to the psychiatrist. She describes the expected developmental sequence for specific psychological functions by which a child's current functioning along a range of developmental lines can be appraised. Progress is typically uneven and specification of a child's position in each line can lead to practical treatment recommendations. An individual child may move along most of these developmental lines "normally," while lagging in one or two.

One of the developmental lines identified by Anna Freud is the line "from irresponsibility to responsibility in body management." Her description of the sequence of this line can be paraphrased as follows.

The first maturational step occurs in the first few months of life; aggression, which has been indiscriminately directed toward the body, is now turned toward the external world. This vital step limits self-injury from such behaviors as scratching, although they persist as remnants in many children at later ages. Movement forward on this line is facilitated by maturation of sensory systems, so that pain acts as barrier.

The next step is advancement in adaptive functioning, such as orientation in the external world, understanding of cause and effect, and control of dangerous wishes—all because of a growing understanding of the real world. Together with the pain barrier and the pleasurable interest in one's own body, these newly acquired capacities are a protection for the child against external dangers, such as water or fire. A variety of failures in development can impede the acquisition of these functions, and the child remains markedly vulnerable and exposed if not protected by the adult world.

Finally, the child begins voluntary participation in behaviors related to medical necessities and general health. Every parent knows that normal children can be remarkably uncompromising and obstructive in health matters. They appear to feel it is their right to endanger their health, and delegate to their mothers all protective and restorative activities. This attitude often continues until the end of adolescence and may represent a residue of the original symbiosis between child and mother (7).

Adolescents' endangerment of their own health is familiar to anyone working with this age group. It demands outside intervention; at the same time, the adolescent vehemently protests the adult intrusion. The nature and timing of the intervention can be difficult to choose. Endangerment of the body can be characteristic of either acceptance or avoidance of contraception or abortion. A counselor's advice must be cast in the light of an awareness of this developmental line, especially if it is ignored by the adolescent. The advice will be attuned to consideration of the adolescent's cognitive capacities and development in other sectors of the personality, as well as hypotheses concerning the unconscious meaning of these self-destructive impulses.

Psychosexual Development

Adolescence is the culmination of psychosexual development during which a heterosexual genital relationship outside the family may be achieved. While this common process seems straightforward, it represents the end result of a sequence of internal and external transformations beset by both stressful environmental events and the impact of any residue of earlier trauma. The first, difficult challenge to the early adolescent is to begin to move sexual feelings away from family members. The love and closeness felt toward family members have previously served as a natural carrier for the sexual feelings and fantasies of the child. By the time of puberty, however, it becomes increasingly apparent to the young adolescent that these sexual feelings are to be directed outside the family. It is usual for adolescents to first utilize their own bodies, in masturbation and its accompanying fantasies, or a friend's body, in homosexual exploration, as paths toward nonincestuous discharge of these feelings. The transition to an actual genital relationship with the opposite sex is gradual. The partner may initially be chosen because he or she shares many of the characteristics of the chooser. As adolescents move away from their own family, much of their emotion is now invested in themselves and their own bodies, an attempt to know themselves and love themselves in a new way. At the same time, favored others, whether heroes, rock singers, or a lover, tend to have features of family members from the adolescent's past. The old, intense emotions and conflicts can now be played out in new relationships, changing attitudes bringing a more successful resolution.

Difficulties with these psychosexual developmental tasks may be visible in situations related to contraception or abortion. Such considerations will be critical determinants of the success or failure of a decision in these areas, even after meeting with a counselor. For example, a young woman who is confused and frightened by incestuous impulses may resolve them by jumping quickly into the relative safety of a series of loveless heterosexual relationships outside the family. A counselor who is unaware of the meaning of this behavior may simply facilitate it by making a contraceptive available. In this situation, it is possible that discussion with her parents, although experienced by the girl as an invasion of her privacy, may clarify family problems and represent the initial step toward helping her understand her frightening and painful conflict.

Separation from Parents

The most public of the adolescent's developmental conflicts is that between independence and dependence. It is the thread running through all interactions with a counselor, because advice is experienced as parental intrusion and no advice as parental abandonment. The mistake that is so easy for any adult to fall into is to accept a momentary decision by the adolescent, because it is delivered with such conviction, as a final position. What adolescents need are firm outside boundaries, so that within them the young person has the freedom to experiment with a variety of identities in attempting self-definition. A teenager who needs to rebel to prove independence should have firm, loving, consistent parents to rebel against and not have to seek these outside boundaries from the police or some other social agency.

This capacity to be firm and straightforward is a necessary feature in a counselor, as well. It cannot be counted on as a basis for immediate gratitude from adolescents, but can give them the time to work things out on their own in a truly independent fashion. For example, the desire to have a child is, for some young teenagers, bound up in the wish to be dependent again themselves. This is a strange idea initially, considering the demand for responsibility and independence young parents will encounter when the baby is born. The clarification of such fantasies can be particularly important when an adolescent is considering whether or not to initiate contraception. Once again, respecting the adolescent's "right to privacy" would mean foregoing the opportunity to observe the adolescent's relations with her parents, observation which may help crystallize the nature of some of the problems which have led to the desire to have a baby. Clarification of family conflicts for the young adolescent may satisfy needs which otherwise would lead to a pregnancy, freeing her to make more knowledgeable decisions about her sexual life.

Summary

The price of an advance on one front is often a loss on another. The liberalization of attitudes toward adolescents is a compliment to the loving care of the parents, to their willingness to adjust their perspective according to the needs of youth. Yet it would be no favor to adolescents if parents were to pull out of the picture entirely when the child reaches the age of fourteen, nor is society helpful when it facilitates such a drift. The parents, imperfect as they are, have invested their care and concern in their children's development, and stand in an advantageous position to make what often seem to be impossibly difficult decisions. This provides the adolescent with a stable environment within which he can gradually test the critical areas of his life, at any given moment, and feel assured that he is protected from premature, irreversible commitments by the patience and wisdom of his parents.

Professional counselors can ease the burden of parents, but not replace them. There are times when it is necessary to maintain an adolescent's right to privacy, but this in no sense implies that it is the standard situation. The many developmental impediments to full knowledge during adolescence make it imperative that a parent or adult advocate stand with the adolescent to offer a perspective less likely to be compromised by developmental limitations. Temporary disappointments will ultimately be balanced by the mature recognition that parents had high expectations of the adolescent, and gave him the time to gradually work out age-appropriate conflicts.

In this time of emphasis on early independence and sexual experimentation, it is instructive to hear the voices of successful adults who developed slowly, but satisfactorily, along these lines. By not prematurely emphasizing one or two personality features, more capacities of the adolescent are given the opportunity to flourish. Jawaharlal Nehru has described his own gradual development; he and his friends at Cambridge considered themselves quite sophisticated about sex and morality.

> As a matter of fact, in spite of our brave talk, most of us were rather timid where sex was concerned. At any rate, I was so, and my knowledge for many years, till after I had left Cambridge, remained confined to theory. Why this was so is a little difficult to say. Most of us were strongly attracted by sex and I doubt if any of us attached any idea of sin to it. Certainly I did not; there was no religious inhibition. We talked of its being amoral, neither moral nor immoral. Yet in spite of all this a certain shyness kept me away . . . (Jawaharlal Nehru: *Toward Freedom*)

Much public attention has been given to patients in psychoanalysis who throw off their inhibitions and give expression to their long-dormant drives, which appears easy and pleasurable. Much less public attention is given to patients who implore the analyst to give them boundaries that were never present in their youth. They beg for instruction and discipline. Their entreaties are not limited to words; their self-destructive behavior is another vivid request for firm discipline from the analyst. Just as we physicians have learned to be more humane and less punitive in helping an adolescent make critical life decisions in areas such as contraception and abortion, we must give firm guidance when necessary, and foster the turn to parents for direction. Helping an adolescent realize the "right to know" entails more than a simple explanation of the relevant medical facts; it means helping the adolescent to keep development open to knowledge and avoid premature closure and its consequences. Yet, on any given day, we as counselors can only follow Horace's recommendation: "Whatever advice you give, be short."

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Rabbinic Comment: The Rights of Adolescents

RABBI DAVID M. FELDMAN

Neonatal defectives and the aged and terminally ill present difficult ethical dilemmas which are heart-rending in their implications, but although the problems of adolescents may be easier to deal with, they, too, can be heart-rending, because the nature, the quality, the direction of a life is determined in adolescence. Questions about whether physicians or social workers have the right and, therefore, the duty to inform parents of adolescent decisions on contraception, on abortion, on drug abuse can also be heart-rending in their consequences.

Assume that these decisions involve practices that are bad. Assume that drug abuse is bad, is not an abuse of the drug but an abuse of the person using them because they destroy character, impair judgment, destroy control of all those sober virtues that are part of religious teaching. Assume also that abortion is bad because it constitutes the taking of a potential life, that it implies at times harm to the young mother—if not physical harm, most certainly moral and psychological damage. Assume that a program of contraception for the adolescent is also bad in itself and in terms of premarital chastity and other virtues. Assuming, then, that these are not matters of indifference, the question is, Should parents be involved by the doctor, the social worker, other health professionals? Do they have the right and, therefore, the duty to inform the parent? As you can guess, I am going to answer the question with an emphatic Yes, then qualify my answer by citing certain circumstances when we cannot be so emphatic.

Parental Responsibility

The question has been put dramatically: "Whose life is it, anyway?" Does the fetus, the neonate, have a right to live, or does that right depend on our stake in it? Does a person of mature years with pain or infirmity have a right to terminate his or her life? Is it his life to terminate or do the rest of us make that decision? In a sense, I submit, the same question applies to the adolescent. They are asking, Whose life (style) is it anyway? Young people confront adults with this challenge, this defiant assertion, so often: "It's my life. I will lead it as I see fit." Then they go ahead to lead it in ways which, to us, are totally destructive. Our response to the adolescent's question must be similar to our response to the neonate or the terminally ill. It's not the adolescent's life to destroy if we believe the lifestyle is destructive.

For anyone to say it is his or her life, that he has the right not to privacy but to live life in his private way as if it has no impact on parents, relatives, and others, is to fly in the face of Jewish morality. That parents have responsibility for the adolescent and, therefore, the right to be involved in decisions, the right to be informed, is fundamental to Jewish tradition, namely, the Jewish conception of family, of the duties and responsibilities that flow in both directions, from parent to children and from children to parents.

This two-way street is expressed in the Talmud in its application of the Fifth Commandment, "Honor thy father and thy mother." We know what children owe their parents, but the Talmud also defines the responsibilities that parents have to their children, one of the first being to educate them. Parents have an obligation to educate their children in the Torah—not just in knowledge of Torah, but in the proper moral, ethical, spiritual precepts, in other words academically, morally, and spiritually.

The Talmud also says the parent has an obligation to teach the son or daughter a trade. Why a trade? Why must parents get children set in

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life with some sort of gainful employment? The answer is that if you don't make sure your child has some kind of gainful employment, then you are responsible for tempting the child to larceny, to a way of life which is the opposite of gainful employment. Part of the responsibility of parents is to see to it that their offspring are put on the right track in this regard as well.

Where does the obligation of parents extend—from birth to adulthood, or throughout life? Is it coterminous with life? Obviously not. There is a time when the adolescent is adult, but when does that begin? There is a notion abroad that at bar mitzvah a child is on his own. A boy at thirteen becomes bar mitzvah (son of the commandment; man of duty), a girl at twelve becomes bat mitzvah (daughter of the commandment). Maturity or majority, becoming major rather than minor, comes earlier to girls. For them it happens at age twelve. A joke current a generation ago among comedians told of the bar mitzvah boy who got up to speak publicly and nervously said, "Today I am a fountain pen." He meant to say, "Today I am a man. Thank you for the fountain pen." But he got his lines mixed up. That may have been funny then because the audience thought he mixed up his lines. But I submit, without fear of effective contradiction, that it would have been funny even to say "Today I am a man." For us to take seriously the idea that at bar mitzvah, at thirteen, a boy suddenly becomes a man is as laughable as "Today I am a fountain pen."

It is important to remember that the term "adolescent" has within it the idea of "escent," of becoming. We're talking not of a state but of a process, which may begin at bar mitzvah or bat mitzvah but which doesn't reach its completion until much later. Therefore, in the Halakha (law), there is another category, another status, the category of *baronshin* (responsible enough to be punished), which the boy does not reach until he is 20 years old. From the age of thirteen, certain responsibilities redound to him: he has to do certain things. He puts on *tefillin* (ritual leather straps worn during prayers). He has to be called to the Reading of the Torah, the scroll of the first five books in the Bible, during religious services. Other *mitzvot* (commandments, good deeds) which apply to women begin with the bat mitzvah, but responsibility, in terms of punishment, of being a *batonshin,* doesn't begin until she's 20.

Interestingly, the Siddurim (prayer books) include a prayer the father makes at the bar mitzvah ceremony: *Barukh shep'tarani me-on'sho shel zeh,* "Thank God for removing responsibility for this child from me." The halakhic (legal) sources explain that, until bar mitzvah, the father has the responsibility for educating the son. Now it is the child's own responsibility to do so. But *onesh* (responsibility) still applies to the father on behalf of the child, because a child cannot really take adult responsibility; parental responsibility for input in what children are doing continues until the end of adolescence. This stands in contrast to the sorry sight that doctors and rabbis witness—parents abandoning their adolescents because the parents are bamboozled by the young over how to deal with the new morality. Whatever the confusion, parental responsibility is clear and definite: to guide, to teach, to point the way for the adolescent. It follows that the doctor, the social worker, all healthcare workers have the concomitant duty to inform the parent of basic decisions on the adolescent's life or lifestyle.

Limits

Now for the qualifications, the reservations. An interesting sixteenth-century responsum which is now part of the code of Jewish law is attributed to Rabbi Moshe Isserles, the R'ma. The rabbi was asked, "Does a child [a man or woman] have to listen to his parents about who should be his marriage partner?" He answered, "No, the duty to respect parents does not extend to this particular decision. You don't have to listen to your parents if they say I don't like the one you've chosen. You don't have to listen if you've made this choice. Because it's going to affect you more than it is going to affect them." The rabbi answered that very crucial question in the negative. His No was later qualified: to what extent did he mean No? "If you choose between one bride and another, all right. You don't have to listen to your parents. But if you're choosing a bride or a groom who is going to bring disgrace or shame on your parents, then you don't have the right to do so. That would be a violation of the Fifth Commandment."

Dr. Abba Borovich has written a remarkable chapter for the medical ethics compendium of the Federation of Jewish Philanthropies on psychiatry and Judaism dealing among other things with adolescents in trouble with their parents. On the assumption that family therapy is better than individual therapy, many practitioners interview both the adolescent and the parents all together. But if the adolescent is going to be so pious as to observe the Fifth Commandment, not speaking freely and telling the therapist what's bothering him about his parents out of parental respect, the therapist can hardly make any progress. What is therefore recommended is that the parents say or intimate to the child, "We waive our right of *kibbud av va-em* (parental respect) for the moment. We give you dispensation to say what is bothering you, so that this therapy session may be of help to you." That is part of the other half of the question; parents must know that sometimes they have to waive their rights or therapy won't be effective.

A rather unconventional statement in the Talmud quoted in Maimonides requires comment: "A parent who strikes his grown child is guilty of a serious transgression, putting a stumbling block before the blind." This refers to a negative commandment in Leviticus which, of course, the rabbis have interpreted allegorically. How can anyone take it literally? How could anyone be so cruel as to literally put a stumbling block before a blind person? So the Talmud interprets the statement figuratively, to mean any kind of misguidance of the unsuspecting. To mislead somebody, to give a person bad-faith advice, to offer wine to one who has taken a vow not to drink wine, to place tempting chocolate cake before someone who's undertaken a diet for that week, all are a violation of this rule.

We're told that corporal punishment, say spanking, of an adolescent, a grown child, is counterproductive; it will alienate the child further from your benign influence and care, and you will be guilty not only of failing to raise the child properly but of having abused your own right of discipline and your effective influence on the child. This too needs qualification. The "big," the "grown" child is not a matter of chronology, but of the child's nature. A pre-bar mitzvah child can be mature, while another child over 12 or 13 can be pretty childish and require more than the usual parental guidance. There is a statutory age for many ritual matters, but the parents' role in discipline must vary with the nature of the child. A parent's undue discipline of a mature child will only push the child over the brink.

The Talmud offers another useful concept, another legal category, that of economic dependency—the son or daughter who lives at home; literally one who "eats at the father's table," an age-free category reminding us that family roles have to do with the child's relationship with the parents rather than the child's age.

My conclusion thus is a dual one. I assert that, from the standpoint of Jewish tradition, parents have a very distinct, definite responsibility for the moral and spiritual well-being of the adolescent, and therefore have a right to all information necessary for decisions with regard to the adolescent. But because giving parents such information can be counterproductive, we need individual alertness by healthcare staff. We need social workers who, after interviewing the parties, will know whether telling parents about contraceptive practices, or about a planned abortion, or about use of drugs will be counterproductive. If the child is an emancipated teenager who, because of parents' input, will only be moved to go further in the opposite direction, it becomes the responsibility of the healthcare worker to decide accordingly. Healthcare workers should be capable of and empowered to determine whether the parents should be involved in decision-making.

Like Rabbi Tendler, I regard myself as first a rabbi, and I want to end with a sermon, or perhaps I should call it an etymologic comment. The word *na'ar* means "an adolescent." Therein lies the sermon. The word is related etymologically to the root *na'er,* "to shake up." A *na'ar* is one in turmoil, unsettled. A child is still in formation, an adult is relatively settled, but an adolescent is in the process of *na'er,* "shaking out." Adolescence is characteristically unsettled, conflicted, astir, and hence difficult. I like what Dr. Young said about adolescents feeling themselves to be adults but not really being adults and, later on, looking back retrospectively and wishing they had had more guidance.

With the verse in Proverbs, I say, *hanokh lana'ar al pi darko,* "educate the young, the adolescent, the child, according to his nature." Adults have to know the person to know whether intervention will be productive or counterproductive. Parents are obliged to give input, but also to determine whether the input will be beneficial or not.

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Transplantation Surgery

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The ethical problems of transplantation have been evolving for twenty years as the state of the art in this dynamically changing medical advance continues to be scrutinized ethically, medically, and in research. Today, kidney transplant is therapeutically accepted and is the most common of such procedures, but transplants of cornea, bone marrow, and bone are also common. Heart and liver transplants are in clinical use, but are still considered experimental; pancreas, thymus, lung, and intestinal transplants are not yet important as therapy but are important experimentally.

Ethicists and religious leaders have debated whether transplants of different organs differ. However, even for organ transplants now being done, such as kidney transplants, what questions are raised, what thoughts challenged?

For example, a 22-year-old patient initially diagnosed as having glomerular disease at age 10 had kidney function of 50% at 11 years which decreased to 20% by age 18. He was on dialysis by age 20. He was a college student whose goal was law school, and he had been accepted at one. His mother, his father, and his sister had protein in the urine. The family's decision was for a cadaver transplantation. What problems evolved and what issues had to be considered from the ethical, legal Jewish point of view?

There are a number of organ sources for this young man—a cadaver, his parents, a sibling, a good samaritan. Is a cadaver kidney acceptable within the Jewish ethical and moral code? Is it acceptable in other religious codes? Do parents have a right or a duty to give up part of their body to their own child? What are the parents' rights compared to a sibling's rights? What of the good samaritan who might walk in off the street and volunteer? We have certainly accepted the good samaritan for transfusions. Anyone can give blood at any given time. But what about a kidney transplantation?

Can one person pay another to give up a kidney? Can a family needing a kidney, knowing there is a kidney available from someone who wants to donate, make arrangements to pay for the donor's funeral or make any financial arrangements with the donor's family? What does that involve?

For that matter, what is death—dependent on the heart beating, or on nonheart function? Do we accept the concept of brain death? Some U.S. states have a law that a person can be pronounced dead with the heart beating; some states still have no laws on what constitutes death. What of the ethical aspect of the U.S. law permitting a person to deed his or her kidneys to someone by a "living will"? In many countries (France, Germany, Sweden), the government has decreed that the kidneys belong to the state and therefore can be taken at death, unless a person specifies beforehand, on a certain day each year, that he or she refuses to give up that right. In this respect, the Jewish point of view might be overridden by the law of the land.

If a parent donates, which parent gives, the mother or the father? Roberta Simmons, in a review of attitudes to donation involving interviews, has noted that 85% of families agree almost immediately that the mother is to give. Why the mother? Does something in American culture or in religious culture deem a mother more important than a father? Or is this choice made because of other cultural values?

Who makes the request for donation and how is it made? If the surgeon makes the request, is there some sort of intimidation involved? Physicians have to be very careful about how they ask for an organ. Medical ethics are involved in asking the parent to donate. How physicians may intimidate by the way they tell the family is most

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important for the person receiving the kidney. It may be a life-and-death matter, but exaggerations may be involved. What is the atmosphere of the request? Does the urgency communicate stronger than the rights of the person being asked? Take the case of a parent talked into giving a kidney to a son as a matter of life or death, typed and rushed to the operating room before being given a chance to think. Is this a reasonable approach to a major problem? It is known that results from a parent donation are extremely good.

Interestingly, in families asked to give a kidney, neither parent is the first choice; usually it is which child should give. Children do take on the parenting role—a child gives to a child. Is that based on culture, or on religious law? Who has the initial responsibility to the donating child? In the United States, the age of the child is extremely important. The parent has no right whatsoever to give away the kidney of a child at any age. The law is very clear that no one can sign anything for a child that is not beneficial to the child. Therefore, even though giving a kidney may not be harmful, is it beneficial? What are the ethical and legal obligations of a brother or a sister? When families discuss donation, it is the general consensus that a brother should give, not a sister. Here is the whole question of the young girl's future potential for motherhood. When the parent donates, the mother gives; whereas when a sibling donates, the brother gives. Can the family give away the kidney of a child? It cannot, except when an identical twin is involved. Here the results are basically totally successful.

Newspaper ads offer kidneys for sale at $15,000 to $20,000. Should the good samaritan be paid? Our society has totally accepted that blood transfusions that can be paid for are paid for. Yet we have been socially strict with transfers of kidneys and other organs. Throughout the United States, laws decree that no financial benefit, no equity whatsoever, can pass between the donor and the receiver. At the same time, good samaritans are encouraged.

What about prisoners? Is an individual who is incarcerated really free to give a kidney? What is the prisoner's ethical and legal situation? The prisoner may want to give a kidney; should that need to give be accepted?

The Helsinki codes on medical research on humans promulgated after World War II decree that no research can be done on human beings unless the procedure is clearly successful and is therapeutic to the recipient; it may be experimental in regard to the donor. This is a very important part of Jewish law; "therapeutic" would relate back to previous success. The use of good samaritans is more and more an issue in the United States because cadaver kidneys are scarce and because good matching, which is becoming more and more important, is difficult. For patients aged 11 to 20, a cadaver kidney has about 55% success. A parent's kidney offers about 60%–68% survival; in the last two years (through October 1980) survival has risen to 90%.

Physicians must judge the medical disability, financial and psychological factors in the patient and the family, and potential quality of life. Which values should take precedence, the patient's or the physician's? Medical decision-making on when and how a transplant should be performed involves questions of the importance of self-care and self-control; of full disclosure of the patient's present condition and future potential outcome.

What does transplantation involve from the Jewish point of view? Is transplantation correct? Are all transplants correct, or are there differences between transplants of heart, brain, lung, kidney? Is there a code dealing with the source of the organ—cadaver, parent, sibling, good samaritan?

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Rabbinic Comment: Transplantation Surgery

RABBI MOSHE D. TENDLER, PH.D.

Dr. Greifer has laid out my task with the precision necessary for transplant surgery: the trick is to transplant a value system from one culture or from one religion to make it universally acceptable. I focus on the universal principles derived from the Judaic biblical heritage.

Once again we need to discuss the equilibrium between "can" and "should." Mastery over nature is a right, a privilege, and a duty. But it is subject to limitations and regulations to prevent one person's mastery over another. Mastery over nature has never been more impressive than it is today. What is more threatening than ever before is that that mastery may lead to disregard for the rights and privileges of humankind.

Four fundamental ethical-moral principles are involved. The first is the biblical commandment *v'chibshuha,* "you shall master my world." This is the human duty and obligation, as well as the human right and privilege. The second principle is the infinite worth of human beings. As the story of Genesis unfolds, God creates a world for only one man, Adam. The divine message is obvious: it is well worth making an entire world for one man. Imagine how worthy man is in the eyes of God. The third principle is that man is not in man's service. God says, "You are my servants, not servants unto servants." Man cannot be used by his fellow man. The fourth principle is the supreme duty to save human lives. This duty implies many things. Most importantly, it implies that God gave forth a world that is run by natural law. We should use natural law to help others. We cannot sit back with easy conscience and say, God made that one sick, let God make that one well. God decided to run his world by his rules. His rules are that he'll make a person sick and you, physician, should make that person well. The biblical reference to save human life is the ethical basis of medical care. Two verses are quoted by the sages: "You must not stand idly by while your friend's life is in danger," and the verse that speaks about returning lost objects. If you have to return a lost donkey, how much more must you return lost health? You cannot say "It's not my responsibility." The natural world was designed by God to require medical ministrations.

In this equilibrium between "can" and "should," naturalness is no virtue. Other religions have made a virtue of the natural, the unnatural being unclean or unholy. The artificial may well be the greatest human contribution, sanctioned by God and welcomed by us. The artificial kidney, the artificial pancreas, the artificial heart, artificial insemination, and artificial respiration are, at the same time, our duty and our obligation as well as our right and privilege. They may very well involve the greatest *mitzvot,* the greatest "good deeds," of a physician.

Mastery over another is an evil, an evil that includes the evil of presuming sole mastery over oneself. We are not our own masters, we do not have the right to suicide, and, therefore, are prohibited from self-injury or self-mutilation. We cannot mutilate ourselves without permission of the one who made us, without observance of ethical principles, without divine permission.

The supreme duty to save human life is to result in a net gain, not a trade-off. Don't substitute one life for another. If we are of infinite worth, then we cannot put a price tag on anyone. Who is to know who is of more worth? We can't even put a price tag on two people higher than on one person. Infinity is infinity. However, there is an ethical principle that says that, even with the infinite worth of each person, I'm a little more worthy.

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The biblical verse "Your brother shall live with you" instructs you to love your brother as yourself, not more than yourself. Hence, you cannot forfeit your life to save somebody else. *The Tale of Two Cities* is not an ethical source book.

If you examine the ethical impact of a medical decision on the donor and the recipient, the physician and society, you can see how these ethical principles dictate specific behavior. There are various types of transplants; particularly, there are vital versus nonvital transplants. We have two kidneys, only one heart, only one liver. Obviously, a vital contribution cannot be made by us, no matter how free we are to make such a decision without coercion. It is forbidden by ethical law, by halakhic principle, by Jewish law. You cannot forfeit your life to save somebody else because you are not in charge of your life to forfeit it. Hence the donation of a vital organ cannot be accepted. That is not open to discussion.

However, an easy distinction between a regenerative and a nonregenerative organ must be made. Bone marrow or blood transfusion are donations that involve regenerative potential. Hence, the risk-benefit ratio is unique, and you can't use the same mathematic formula for it as for nonregenerative transfers. In bone marrow or blood transfers, the risk is much reduced, assuming that the method of obtaining the blood or the bone marrow doesn't involve great risk. Hence, you find yourself in a situation which I can best describe by citing the examples given in the Jerusalem Talmud. Someone is drowning in your swimming pool. You have a long pole in your hand. Not to put that pole out to save the drowner is a passive act of murder. Or say a storm rages off Fire Island and you're on the beach. You see a fisherman's boat overturn and you're a pretty good swimmer. Should you jump into the ocean and swim out to him? Will you reach him? If you do, will he pull you down? These are two distinct examples of standing idly by. In the first, you're a murderer for not putting out the pole. In the second, you are properly exercising your priority over all other lives by standing on the shore and reciting a prayer rather than jumping into the water. This is the distinction.

Analyze what bone marrow transplant means. From 100 punctures of the iliac crest, nothing much is going to happen postoperatively, unless infection occurs because the physician forgot to wash his hands, which is unlikely. However, general anesthesia is a real danger. For a healthy person, the donor of the bone marrow or the kidney, the risk of anesthesia is somewhere around 1:4000–5000. Counterpoised to that risk is someone who's certainly going to die. Then the analogy is closer to the swimming pool than to the raging ocean. It is a proper risk to undertake to save your fellow man.

Some people would say, I don't want to risk even a 1% danger. They could be faulted on ethical principles. You would have the right to encourage them, to placate them, to cajole them, to explain to them, but not in any way to coerce them, even when there is only a slight danger, and certainly not when there is significant danger.

Experimental transplants present a rapidly changing picture. Cardiac transplants require another look. Are they classifiable as therapeutic procedures or as experimental procedures? Based on the results of Dr. Norman Shumway's team, heart transplant should indeed be classified as therapeutic, not experimental. The heart is obtained post mortem, but giving up a kidney entails significant risk, more than just the risk of anesthesia. Postoperative complications as reported in a study of 300 living donors in 20 years of kidney transplants at Peter Bent Brigham Hospital encompassed 16 major operative complications, including one death, five wound infections, five pneumonia cases, one acute renal failure, and one psychosis. Worldwide, only five deaths caused by kidney donation have been recorded. Hence the risk, from a moral-ethical Jewish point of view, is manageable. It may not be one that compels you to donate. It is not exactly the swimming pool, but it is a manageable risk. Bone marrow and kidney donations are within that level of risk we are permitted to take.

However, motivation is an acute question. The purchase of organs poses a real problem. It's one thing to speak about a kidney transplant and another thing to find a kidney for somebody, let alone an organ supermarket, as in the novel *Coma*, in which organs of compatible types hang in a freezer with perfusion tanks. Selling human flesh in a supermarket strikes us as somehow wrong, but is motivation that is not pure altruism really wrong? I've yet to see an altruistic hospital administrator. They send the bill regularly, and even a surgeon who may have been most altruistic in giving sleepless nights to becoming a great surgeon does not live in the slum area of town and expects to be paid for work. What is wrong with a donor saying, Yes, I will subject myself to discomfiture, to the risk of kidney removal, but I expect to get paid for it, that's what I do in my normal life. I break my back to earn a living. I attend meetings and come home at three o'clock in the morning on a snowy night and risk my life traveling the highway because I have to earn a living. What's wrong with getting paid to risk my life?

Yet the sale of human flesh doesn't sound right. I don't believe any ethical principle speaks against it, but I have a gnawing fear that one day I'll see a big section in the local newspaper listing histocompatibility types and prices, or an advertisement for an auction of a kidney. Escalation is a problem, but paying for human flesh donations cannot be ruled an evil. Certainly a donor deserves remuneration for loss of earning power during the time in hospital. A donor may well expect others to pay for insurance to guarantee that if the one remaining kidney fails, the donor will get a kidney transplant free. These things make sense. Basically, the Jewish point of view raises no objection to payment for organ donations.

Another question: What would it mean to a child to be a donor? The guarantee of success for donation by an identical twin is very high. What would be the psychic trauma to an adult who learns that he or she could have but did not save a sibling's life by donating? Is future trauma enough justification to subject a child to pain, risk, and the discomfiture of surgery? It is an intriguing question, but we can only volunteer to donate ourselves. We cannot donate anybody else. Your child, whether you like to admit it or not, is a "somebody else." Therefore, surely it is best for society that children not be used as donors.

The issue of when death occurs is critical. The idea that a person is dead when brain death occurs but while the heart is beating is a strange one to sell to Jews, as to Catholics. Catholics, however, have made their decision, since they have a pope who can make infallible decisions. In the Fox case, the pope ruled that in a patient who has independent respirations but for whom there is no hope of cure, it is permissible to stop all treatments, to disconnect the respirator. The question whether a patient who is brain-dead is dead is thus moot. From the Jewish point of view, a patient who has only cerebellum left, who still has independent respirations, must be treated as a live person entitled to all the care and concern of the medical profession. But a patient who is brain dead, with total cessation of brain function from the medulla up, is truly dead. To that person the physician has only one obligation: bury the body as quickly as possible. Consequently, a true brain-dead person is a proper source for organ donation if the person had willed it so in life.

From the recipient's point of view there are many other factors. The risk of transplant versus the certainty of fatality without transplant allows the recipient to assume greater risks than can the donor.

One concern has never been discussed properly. You are a physician with a patient on dialysis, and you know from the patient's record that he can be maintained comfortably for two years without detriment to his welfare. A kidney becomes available after half a year. You had the patient typed, histocompatibility results come in, and you could transplant him. But transplant involves many more risks than dialysis. Consequently, taking into account not only the risk of surgery but the risk of immunosuppression, infections, and quality of life during the period of organ rejection and counterrejection, should there not be an ethical principle that says, Keep a patient on dialysis as long as the patient can take it? That is, as long as the patient is not "climbing the walls"; in Jewish law, psychological stress is as important as physiological stress. This principle basically addresses the risk-benefit ratio at any one moment.

The physician-related factors I find to be both troubling and exciting. When is the physician sure that clinical use is justified? With the kidney, clearly. How about lung, liver, or endocrine; what about testes and ovary? The principle discussed in the section "Beginning of Life" applies here. When you do your homework, you can go clinical, but you had better do your homework. Steptoe and Edwards were criticized because they didn't do their homework, at least they didn't publish the homework they did. If you moved from rodents to dogs, from dogs to monkeys, you know what you found, you did enough experiments, you really have a right to rely on the biochemical or the biologic common denominators. You have a right to make the leap of faith which is part of our right to try to master nature. As long as you've done all that you can, you can expect that God will help you out. We assume he won't lead you astray and, therefore, the jump from laboratory or experimental to therapeutic or clinical use, although it involves a leap of faith, must also involve much rational judgment.

A more serious problem is when to retreat from clinical use. The issue of heart transplant is most disturbing. Transplantation continued too long after poor results should have led to cessation of all heart transplants. It did ultimately, and now the idea has picked up again. Most disturbing is the evidence that known immunogenic factors, histocompatibility studies, were disregarded by all investigators except Shumway et al. I have no doubt that they achieved better results, even initially, by doing their homework better than anyone else. Indeed the results to date, approximately 50%–65% survival for more than two years, has moved cardiac transplant from the experimental into the therapeutic arena. But even more troubling is when do you back off after you're quite successful. A new published study shows that immunogenic factors, new subtype antigens, are very critical. Matching with these DR antigens gets top-notch results. There are new techniques for immunosupression to increase transplant success—presurgical transfusions, Cyclosporin A, antilymphocytic serum, antilymphoblastic globulin, TLI, total lymphoid radiation, renewed interest in thoracic duct drainage.

It's hard enough to find ourselves in a garden from which God says you may eat of all the trees except one. It's doubly difficult if he tells you to stop eating from the tree you were allowed to eat from before. In cardiac transplant or kidney transplant, if a patient can be maintained by dialysis or by conservative management, maybe the rule now should be to stop all transplants. Let the fruit ripen a little bit. Give the patient four, five, or six months. See what the next published study offers. If it holds up, treat the patient differently. Why rush ahead? Only if the patient's life is in danger and he'll die tomorrow must you decide now. Doesn't this waiting take advantage of human mastery over nature?

In Britain and the United States, no statutes have been formulated for living donor contributions. In Italy, living donations are legally restricted to the kidney; in France and Australia, legislation does not limit the kind of transplant but merely specifies the definition of "free of duress." In the United States, cadaver organs removed by a coroner may be used for transplantation without permission of the family. Clearer legislation is obviously needed. Not everything that is legal is ethical and moral. But certainly ethics cannot disregard the legal, and there is some comfort in obtaining the opinion of society as expressed by legislation to know how far we can go by law. Society's responsibility to offer special care for the donor seems also to be an ethical responsibility. Society should protect the donor of a kidney who is in need. In my opinion, part of society's responsibility to the donor is Medicare or Medicaid coverage; with coverage, the chances are there will be more donors—which we are seeking.

The most serious problem of all today is the problem of triage. What do we do when the infinite worth of each of us is given lip service, but finite social resources are the facts under which we live? How do we allocate scarce medical resources when transplantation surgery, for example, costs $50,000–$100,000 per patient? Where do funds come from? What are our priorities in our society?

Inherent in the Jewish point of view is an expression of confidence that decisions on these great issues do not reside in heaven. We don't accept an infallible, irrevocable voice from heaven to clarify even these complex ethical issues. This is, of course, a disadvantage that we have compared to other religions. Using the biblical ethical principles that I have outlined may help us all, while we study the problems with integrity and devotion, to surely reach the proper conclusion, one that is pleasing to us and to God.

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Risk-Benefit Ratio: Hazardous Surgery and Experimental Therapy

FRED ROSNER, M.D.

In Jewish tradition a physician is given specific divine license to practice medicine. According to Maimonides and other codifiers of Jewish law, physicians are obligated to use their medical skills to heal the sick; patients are also obligated to care for their own health and life. We do not have title over our lives or bodies. We are charged with preserving, dignifying, and hallowing our lives. We must eat and drink to sustain ourselves. Similarly, we must seek healing when we are ill.

Another cardinal principle in Judaism is that human life is of infinite value. The preservation of human life takes precedence over all commandments in the Torah, with three exceptions; avoiding adultery, murder, and incest. Life's value is absolute and supreme. Thus, an aged man or woman, a mentally retarded person, a deformed baby, or a dying cancer patient all have the same right to life as you or I. To preserve a human life, even the sabbath and the Day of Atonement may be desecrated. All rules and laws other than forswearing the three sins are suspended for the overriding consideration of saving a human life. The corollary of this principle is that one is prohibited from doing anything that might shorten a life, even for a very short time, since every moment of human life is also of infinite value.

The problem is to weigh, in Judaic terms, the possibility of shortening even the brief life span of a terminally ill patient against the possibility of cure or prolonged survival if a hazardous treatment or experimental procedure is attempted. Given an extremely ill patient whose prospective life-span is very short, perhaps only a few days or weeks; and given a therapy or treatment method which, if successful, would allow the patient to heal and to live for a prolonged period, months or years, but which, if not successful would cause the patient to die immediately, how should physicians conduct themselves in such a case? Should they risk the definite short period of life remaining for the patient by administering the drastic remedy with the hope that the patient may be rescued from danger and live for a prolonged period? In other words, should physicians abandon the patient's definite but short life span in favor of the possible significant prolongation of life by the administration of this hazardous treatment?

This difficult problem confronts not only the physician but also the patient and the family. They too must be able to decide this question, which is not purely medical. Is the patient allowed to accept hazardous surgery or experimental therapy? This is a basic decision which includes medical, moral, and legal aspects. We must provide a definitive decision from the viewpoint of Jewish law and ethics for the physician, the patient, and the family.

An illustrative case exemplifies the problem. A 9-year-old girl with acute lymphoblastic leukemia, treated with the best chemotherapeutic regimens available, fails to achieve remission of her disease after eight months of treatment; further chemotherapy is thought to have less than a 5% chance of success. She has a very low white blood cell count and is in constant danger of developing serious, even life-threatening infection. She also has a very low platelet count and is in constant danger of serious bleeding. The pediatric hematologist suggests bone marrow transplantation as a final resort. Tissue typing is done and the father of the child is found to have the same tissue type as the child. The chances for a successful bone marrow transplant are thought to be about 60%. However, the procedure itself is

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associated with a 25% mortality and a very high morbidity. Most patients suffer from a complication called graft-versus-host disease in which the donor bone marrow—in this case the father's—causes serious and sometimes fatal signs and symptoms in the recipient, the child. Without the transplant, the child may have no chance of remission or cure, and her life expectancy is thought to be weeks or, at best, months. On the other hand, long remissions following bone marrow transplants for acute leukemia, although unusual, do occur in perhaps 20%–25% of patients.

What are the moral and ethical issues raised by this case? The child is 9 years old. Does age play a role in deciding whether bone marrow transplant is sanctioned in moral teaching? The disease afflicting the child, acute leukemia, is invariably fatal if untreated. Therefore, not to treat seems to be an unacceptable approach in view of the supreme value of human life. However, this patient was treated. The best chemotherapeutic regimens were used and were unsuccessful in arresting the disease. Now we physicians are faced with the possibility of employing the highly risky technique of bone marrow transplantation, with the risk-benefit ratio I have cited. Does Jewish law recognize the concept of risk-benefit ratio? Does Judaic moral teaching consider the statistical probability of prolonging life versus the mortality rate or the odds of shortening life? May a hazardous therapeutic procedure be instituted in a dying patient if there is a slim chance of cure, even though the chances of survival are much less than even? How does one define "slim"? Is a bone marrow transplant a recognized, accepted, widely used modality of treatment, like a kidney or an eye transplant, or is it still highly experimental? Should one differentiate between therapeutic approaches that are hazardous, and hazardous procedures that are entirely experimental?

The use of certain drugs—daunorubicin, cytosine arabinoside, vincristine, prednisone, asparaginase—to treat acute leukemia is certainly fraught with hazard because toxicity is considerable. However, the efficacy of these and other chemotherapeutic drugs is also well known. Chemotherapy is able to produce long survival in about 60% of children with acute lymphoblastic leukemia. We, as physicians, administer these drugs in anticipation of a cure, despite the known risks and side effects. Should we sanction such risks in the use of a new experimental drug or procedure such as bone marrow transplantation, whose cure-rate potential is not clearly known?

In the case at hand, may the child undergo the bone marrow transplantation? Must she undergo the bone marrow transplantation? Is marrow transplantation therapeutic or experimental, or both? May the doctor offer this form of hazardous treatment? Must he do so? Does Judaism have a discretionary or mandatory attitude toward procedures that involve significant risk? What is significant risk? Would our ethical teachings sanction bone marrow transplantation in this case because of the life-threatening nature of the underlying illness, even though the procedure itself may lead to the early death of the patient?

Numerous other ethical questions are involved in this case. If the procedure is sanctioned, is consent required? From whom? May the father subject himself to the danger and risk, albeit small, of serving as a donor? If the child dies following the transplantation, may an autopsy be performed? Theological and philosophic questions can also be raised by this illustrative case. If God ordained that this child should die at age nine of acute leukemia, how dare we, as physicians, interfere with God's will and attempt a bone marrow transplant to cure the child? How can we, as physicians, add harm over and above the harm produced by the disease itself? If physicians cannot recommend a specific experimental treatment or procedure on the basis of sound scientific principles, may they offer it as a one-in-a-million chance? Would Judaism prefer an approach in which a patient is left to chance?

I return to the basic tenet of Judaism that I enunciated earlier, the supreme value of human life. This principle is based, in part, upon our belief that we were created in the image of God. Therefore, when a human life is in danger, even when there is no hope for prolonged survival but only for very short term survival, all commandments of the Torah are set aside. Any act which can prolong a human life supersedes all the commandments of the Torah except the three cardinal ones. What do we physicians do in this case? I ask Rabbi Tendler to discuss and answer, if possible, some or all of the ethical and legal questions I have raised concerning risk-benefit ratio in hazardous treatment and experimental therapy.

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Rabbinic Comment: Risk-Benefit Ratios

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After that brilliant dissection of the ethical issues, nothing is left for the rabbi to add to what the hematologist has said, except possibly a discussion on the origins of the Kupfer cells in the liver; a recent *Science* issue reports they begin in the bone marrow. To answer the questions posed by Dr. Rosner, I could just say: Yes, No, Yes, No. However, I would like to approach the same topic from a slightly different vantage point, one which lays the foundation for a Yes or a No.

At issue in any high-risk procedure is, first and foremost, the concept of the physician-patient relationship, or more accurately, the definition of the words "physician" and "patient." A physician is not a physician any time he or she feels like being a physician, but only when he has a patient. Not every patient who lays down in bed is a patient. Some patients should be at home. They don't belong with a gastroenterologist; they are having trouble with their spouse, not their colon. Some should be in the chapel, not the hospital. Sometimes physicians are confused about their patient and, hence, present issues for solution that don't lend themselves to solution. Theologically, we are aware of the dilemma.

Medicine in the Realm of Natural Law

It would seem that the fundamentalists, such as the Christian Scientists, have with greater integrity analyzed the proper role of physician and patient. The patient is subject to God. The physician opposes God's will. Get rid of the physician, leave the patient to God. It is a simplistic approach and one that should be understood in the light of Jewish tradition. It is our Jewish understanding that God sent forth a world that runs by natural law, and by natural law humans get sick. God instilled in us human wisdom, including the ability to cure and the ability to invent new and better cures as the years go on. God indebted us to be at the service of our fellows in need. In the language of the sages, if you are required to return a lost object, surely you must return lost health. If, indeed, it is forbidden to watch your fellow human drown from the shore when you could throw out a lifeline, surely you cannot watch another human in illness when you know how to cure it, and yet withhold such cure. In both ethical situations, the physician is compelled by ethical law to intercede by God's direct command.

Hence, Jews see no adversary relationship between physician and God. We merely have a question. God, why did you set up the world this way? Why did you leave for yourself certain theologic prerogatives while asking us to make believe that the world is run by natural law and that we are committed within natural law to function, indeed obligated to act? Obviously, there must come a time when the doctor or the patient seeks help or solace outside of natural law. Faddism, superstition, medical approaches that lack a rational underpinning fall out of the framework of natural law under which the physician services others. Neither physician nor patient can go outside natural law for fear that an adversary relationship with God is being set up. The physician can only function within natural law, which is rational and understood.

When a doctor says, "I don't know what to do but let's try something anyway," that physician is functioning outside the realm of the physician. He is not behaving as a physician. For this action, he has no patient. When the patient has been to twenty doctors and wants to go to a twenty-first not because doctor twenty-one is better, but because twenty-one is his lucky number, then he is acting outside the realm of a patient. He is seeking help outside natural law. Such help is not available to him. Such help was not intended for him.

What are the ethics when a doctor with integrity says, "I don't really know what to do because to know what to do means to offer help to the

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patient. I am not convinced this particular treatment will help, because it often doesn't. Sometimes it does, but I have no way of knowing whether this patient will respond with a benefit or a deficit, whether this patient is one of the 30% who I will cure or one of the 70% who I will kill with this treatment." The first question to be asked is: "Am I functioning within the boundaries of natural law? What is the winning number in the game that allows one treatment modality into the legitimate pharmacopoeia and keeps another out as faddism?" The winning number is really a composite number that has to do with many factors, including how much pain the patient has, his or her family relationships, social needs—the cost of treatment to society and whether society can afford to offer it to this patient. Put that all together in any one case, and it is possible to decide.

It is a daily occurrence for a rabbi to be consulted by a patient and a physician in cases like Dr. Rosner's. Dr. Rosner cited a 40% chance that the child will die of a graft-versus-host response, 60% chance Dr. Rosner would do some good, and 15% chance that he'd do a lot of good. What do you say, rabbi? Is this within natural law or outside natural law?—for that is the question. Analyzing the question to its fullest and deepest, what really is being asked is, When do you treat and when don't you treat? Are there patients that should not be treated? Most physicians, when it comes to nontreatment, subjugate ethical and medical considerations to legal concerns about abandoning a patient. The doctor may very well not want to treat this patient but is compelled to continue treatment long past the point of no return. The problem at this time has no solution.

But are there guidelines to determine which patient should not be subjected to treatment? I present four situations in which the possibility of nontreatment arises and then analyze the one in question, the risk-benefit factor in nontreatment. First, the patient who is neurologically dead. A decision has to be made: Is this patient dead and no longer subject to ministrations from the housestaff? It is clear to me that brain death, as defined by the Harvard criteria—total cessation of brain function—means the patient is not a patient and is not subject to any medical ministrations.

The second case is the patient with intractable pain, for whom the benefits to be achieved by treatment are only temporary prolongation of life or, as some ethicists would put it, postponement of death. Intractable pain without hope of cure is a reason for nontreatment even when treatment is easily available within natural law, as a so-called tried and proven treatment. The benefits to be achieved are not worth the risk involved. The risk is not risk of death. The risk, or the price to be paid, is an unacceptably pain-filled life. If such situations still exist despite the advances of neurosurgery and pharmacology, there is adequate reason not to treat a patient who does not want treatment because of intractable pain. There are adequate biblical references for this conclusion.

In the third case the issue becomes most difficult. Postponing the patient's death will not mean intractable pain, but the treatment involves risk without hope of long-term survival; the ravages of the disease are such that the patient cannot survive for long. Here, the numbers game comes in—how long is "prolonged"? The definition that some physicians use for "terminal patient" is that, in medical opinion, the patient will not survive beyond four to six weeks. Such a patient can be treated and should be treated, if the treatment involves no significant risk. If there is risk to the patient, even a 25% risk of fatality from the treatment, and the benefit to be gained is only a prolongation of life of a month or so, the clear biblical evidence is that the treatment should not be given unless the patient demands it. Then the issue would be the psychological trauma of refusing treatment. For that reason alone, the treatment would have to be given. Treatment that will prolong life only at the cost of significant risk to the patient is not in the realm of natural law in which the physician can function—not because the treatment is outside natural law, but because the patient is no longer a patient. A patient is your patient to suffer risk when you are a physician who offers a cure. Again the numbers game arises. How much risk? Why 25%, how about 22%? I speak only from case law, from cases that have been so decided by authorities in the field.

The fourth case, triage, I keep hoping will never be necessary; but it exists. Is needing the treatment for somebody else adequate reason not to treat a patient? I hope no physician ever gets caught facing two people dragged off the West Side Highway on a Saturday night when all but one respirator is in use—two people need the one respirator that is available. Such are the soul-searing decisions that physicians have to make, day in and day out, when it comes to beds in intensive care units (ICU). I'm close enough to medical practice to know the magnificent work that's done in ICUs as compared to other hospital rooms. Clearly, someone in the ICU bed has a far better chance of survival than anyplace else. There are not enough ICU beds to go around. In fact, you physicians are practicing triage.

Before the federal law providing free dialysis service to anyone who needed it, a law that Dr. Griefer had much to do with, "God-squad" committees decided who did and who didn't get dialysis; I sat for a few weeks on such a committee. Five to six thousand patients died each year in America for want of a dialysis machine. Triage was the reason for withholding treatment. I hope that the guideline given in the Bible—that the greater scholar deserves more concern than the lesser scholar—will never have to be used. I would not want to decide on the basis of a person's scholarship who deserves the dialysis machine, or the ICU bed, or the respirator.

Medical students I have worked with say to me, "We are trained to help, to make a patient who isn't breathing breathe, a bleeding patient stop bleeding. We don't analyze the ethical issue of whether or not this patient should be treated. If we did, too many people would die. We need a Pavlovian response. If there's a person in need, I'm the one to help. It is only the rabbis who have time to sit around and study what to do in such a case." But a time will come when instantaneous reactions will not be possible because the treatment modalities won't be available for everyone.

Dr. Rosner's Case

In the case cited by Dr. Rosner, what are the ethical issues—those raised by Dr. Rosner, and a few more?

Who Should Decide? I think the first issue that we've been skirting is, who is the captain of the ship? Who makes the decisions? Some people solve their own problems. They call the rabbis, they are oriented to family tradition, a serious decision requires rabbinic intervention; they have no problems. But what should society do? Who should make decisions about which treatment should be offered or not offered? Who decides whether the risk is too great for the benefits, whether the benefits warrant the risk?

What has become one of the great landmark decisions in medical ethics is the Sakiewiez decision in the Massachusetts Supreme Court. The court decided that neither you nor I should decide, but that the court should decide. This issue is fundamental and impacts on the ethical roots of our society. Only society can decide, and society speaks by legislation. The courts speak the will of society by administering laws in accord with the will of society. It is a stand that cannot be faulted, but God forbid decisions should work that way. Anytime you have a decision to make in the emergency room or the operating room, will you call the court? Then will you call your lawyer to file a brief?

The mechanism is lacking for *Sakiewiez* to work, although the theory is there. Some issues are of such ethical import that a doctor cannot be trusted to make the decision because even a doctor is only a person. The decision is fundamental to the survival of our society.

All of us involved in a case have to contribute to medical decision-making by throwing our data into the computer and seeing what comes out. Nevertheless, I must raise a practical issue that may come up for elucidation in discussion later. The role of the guardian has been, for me, one of the most troublesome points in medical ethics. How often is a husband declared the guardian of a wife who he abandoned four months ago? How often are parents the guardian of a child admitted to the hospital last year for battered-child syndrome? How often is a child the guardian for a father he has neglected for twenty years?

The legal assumption in our society that a guardian has special rights should be seriously questioned. In fact, in the Jewish view ethical decision-making is not reserved to the parent, who has no special prerogative in medical decisions for a child. The parent's opinion as an interested, concerned person should be considered. But the parent's conscience and the parent's intuition must be weighed by an objective yardstick of right or wrong. Although the legal system gives special prominence to the opinion of the guardian, the ethical system based on biblical law does not.

Experiment and Clinical Use. The experimental nature of medicine is the next fundamental issue. When is a drug or a procedure experimental, when should it be used on humans—when do you "go clinical"? How does a medical researcher justify a Phase I study? A Phase I study is preceded by animal work; the previous patient was a beagle. What justifies the great leap of faith from a beagle to a human? In Jewish ethics, the human mind, the spark of divine intelligence which we speak of as the "godly image," is a functional spark. When a researcher has done the homework, gone through all the beagles, spoken to all the people whose opinions he or she respects, he then has the right to go clinical. He then has a right to say that, by natural law, there is an approach that may be of help to humanity.

Rational and Irrational Risks. What about the risk? Put it to the simple test: If I do not treat, what will happen? Will the patient die inevitably? If death is inevitable, then clearly the risk I'm prepared to take (and it must be a rational risk) is very great. I often ask the physician, perhaps a neurosurgeon, consulting me, "How much money would you invest in stock with these odds?" A doctor who tells me there's really no hope for this patient, the chance is 1:1,000, 1:1 million, has left the realm of natural law. Natural law is natural science applied by rational people. If rational people don't waste their money on a 1:1,000 risk, they should not waste someone's life on a 1:1,000 risk. In such high-risk surgery, the surgeon often remarks, "Rabbi, you pray and I'll do the surgery." My usual answer is, "If you need my prayers, I can pray so well the patient'll get better without your surgery." I don't want a surgeon who needs my prayers. A surgeon has to be confident enough without my prayers. This is the test. Irrational risk-taking is called murder even if it occurs on a surgical table, in an aseptic surgical theater.

What is sensible risk? Calculating it is complex, but surely any risk estimated at 1:100 we do not accept. A risk of 10:100, or 20:100, and cure is a possibility, we do accept. When cure is not in the offing, the risk has to be very, very small. When no hope for cure exists, risk is not easily justifiable.

Two cures are possible: one that cures the patient, and another that palliates the condition so that the patient's life is "cured" for some period of time. You can subject your patient to a significant risk when no cure is possible but the outcome will at least be palliation and relief from pain. Pain relief is something we're willing to pay for, for God did not intend us to live in pain. This is the fundamental analysis from primary biblical literature.

Some societal concerns for research that affects large numbers become less significant in a one-physician–one-patient relationship. Large-scale research decisions often undermine fundamental tenets of society. Here are some scary protocols.

In the Barber study, hypothetical cases worked out by professionals so that they appeared to be real protocols were posed to 293 of the leading human research directors of hospitals and institutions. The one protocol that stuck in my mind as disturbing was a protocol in which thymectomy was offered by random selection without patient consent to children undergoing heart surgery. The purpose of the research was to determine whether a thymectomy would be advisable in transplantation cases, to prolong the life of the transplant. Mind you, nothing was wrong with the children's thymus glands; this was 1977, when people knew that the thymus gland is involved in general immunology. Only 72% rejected the protocol as an unacceptable risk for the benefit to be achieved; 28% approved it without reservation. This means that 28% of the people who may treat 28% of the patients of the world were willing to subject their patients to this risk without patient consent—for that is how the protocol read.

I was recently asked to comment on a protocol to be performed in New York City in which a cardiac bypass operation was proposed for asymptomatic patients—no pain, no angina—with coronary artery disease identified in routine examination. These patients were to be subjected to three catheterizations, then to the bypass operation, to learn whether the procedure would prevent sudden coronary death syndrome. Most of the medical people supported the protocol. Ethically, such a protocol is unacceptable. The risk to the individual patient, based upon knowledge, homework, available to everyone in the scientific literature, was unacceptable.

In the Barber study, only 6% of the 293 respondents claimed to have attended a lecture series longer than four hours on any issue of medical ethics. That is a real concern. Major research projects, involving hundreds of people and large commitments of social funds, can indeed undermine basic social tenets. Experimental treatment is justifiable only with good risk-benefit ratios, which means excellent benefit with minimum risk. When the benefits are less, the risk must also be less.

In the real, not theoretical case of the child Dr. Rosner asked about, for whom painful treatment offered 60% chance of remission and 15% chance of long-term life saving, with a prospect of the graft-versus-host response—which is not pleasant to see—the decision was to approve the treatment. I don't think I would vote the same way again. I would be more negative. In several later, similar cases, none of the patients have benefitted greatly from treatment. I begin to question the homework that was done.

The ethical dilemma is clear to those who attended synagogue last week and this week, when the reading of the book of Genesis began. Genesis records two sins. The sin of Adam was to eat of the tree of knowledge. The sin of the builders of the tower of Babel no one understands. They built the tower and tried to fight with God, or so the story goes. Our Jewish tradition tells it differently. God told us, go out and conquer my world; invent new medication, divert my streams, uproot my mountains. It is your world. I trust you to do with it as you please. But these people, who had it made, refused. They decided not to expand horizontally but to build a big tower vertically and stay a closed society. God considered this a violation of earthly natural law and punished them. This is our dilemma. Adam was told: you can eat of all the trees of the garden, but for one tree—keep your hands off. We can function in this world only under licensure, only with limitation. The people of Babel limited their lifestyle and didn't want to invade the world too greatly. Both sinned. A doctor who says I will not take advantage of the advances of medicine because the risks are great falls into the dilemma of the Tower of Babel; and a doctor who thinks he or she really knows how to cure a patient is guilty of the sin of Adam.

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Adolescence to Adulthood: Discussion

MODERATOR: DONALD GRIBETZ, M.D.   DISCUSSANTS: Rabbi David M. Feldman, Ira Greifer, M.D., Fred Rosner, M.D., and Rabbi Moshe D. Tendler, Ph.D.

Questions were posed by members of the audience and were read by the moderator.

Question: What does the ethical Jewish parent do with the sexually active nonmarried adolescent?

Sexually Active Adolescents

Feldman: The answer requires a case history, to know who is involved, which son or daughter. The Jewish legal, moral stance on premarital sex is that it is a no-no. Adultery is very serious. Nonmarital sex is not as serious, but is certainly immoral from the Jewish point of view. It is a violation of sexual purity and of the marital structure. There is also a difference between long-term sexual activity and a one-night stand, a short-lived departure from the ethical norm. Being sexually active is not a short-term departure but a long-term matter of lifestyle. The parent has the right to say, "This is not to my liking. Together we have to find a way to see my point of view. If you don't see my point of view, listen to my direction." Again, I can only answer what the Jewish point of view is, I certainly cannot advise on how to deal with a particular child. But we adults should keep our eyes open, since the behavior might not be the lifestyle of the adolescent. Physicians are used to looking for symptoms. In a sense, that is what we should do, look for signs of unhappiness. Whether the adolescent is particularly aware of the unhappiness at first, who knows. But you can imagine situations in which an adolescent—around 16 or 17—would be very sexually active. That might not be what most adults would think is best for someone of that age. The adolescent could be in different relationships and could also be actually capable of a sustained sexual relationship leading to marriage but be having trouble because others are not ready, and the adolescent has to break off. This is indeed a complex question. We might have to know all the particulars. What is the age of the adolescent? We should keep in mind that it might be, for that person, a happy, productive, mentally healthy kind of life.

"Going Clinical"

Question: Dr. Greifer, when do you "go clinical" and recommend new medical technology?

Greifer: At what point do you say you do not make available to the population, to our patients, the best of the state of the art in medicine, the treatment which is best, which is 100% the day you give it? Only in retrospect is the treatment you've given "half" technology—half the available state of the art. Therefore, when transplantation or dialysis is offered to someone, the risk-benefit ratio for quality of life must absolutely be told to the patient. But when are we ever at the point of full technology?

Tendler: The patient tells you. Transplantation teams do not wait for the "final solution." But you should watch your patient. As long as your patient is doing well and accepts alternate treatment, observe the first rule of medicine—"keep your patient from the surgeon." The patient will tell you when you should decide to move to the alternate treatment modality. The patient may begin to deteriorate or you may think you've gone as far as you want to risk the patient under the treatment schedule. It is a question of taking advantage of the science of the time. It is a question of saying we have two sciences at the same time. Therefore, one of the sciences may evolve very rapidly, two weeks may make the difference.

Three transplantation centers don't use certain current techniques although there are reports that they are clearly advantageous. What is new and what is old? Thoracic duct drainage became an old technique and was discarded. Now it is back as the greatest thing since 7-Up was invented. This is the nature of medical progress.

Jehovah's Witness Patients

Question: What are the obligations of the physician to a patient who is a Jehovah's Witness and decides he does not want care even if that means he will die? How far do you go to implement your code of ethics and morality in such a case?

Tendler: I was just involved in a case at a small local hospital where the doctor decided to do surgery against his best judgment because the patient refused transfusion. The patient clearly would have been transfused were it not for religious objections. So the patient underwent surgery and managed to recover. However, the legal consequences of the patient not pulling through are horrendous to consider. Here, the issue is not moral and ethical because, morally and ethically, there is a simple answer. Unfortunately, it is a biased answer. I don't accept the Watchtower Society interpretation of the Bible verse "Thou shalt not eat blood." Because I believe they are in error, I don't have any objection to fooling them into accepting a blood transfusion. If there are no legal consequences, it would be morally and ethically acceptable to put them under anesthesia and give them a blood transfusion and not tell them about it. This, of course, isn't the case.

There is enough legal precedent in New York State Supreme Court to give you both answers. Some have supported the right of a Watchtower member to die—and they have—if the Watchtower member was an adult, not a minor. In almost every case involving a child, they have declared the child a ward of the court and have allowed the medical care that was indicated. The tendency now, over the last ten or eleven decisions, is in favor of letting people decide on the basis of their religious beliefs if they want to live or die. From a moral and ethical standpoint, I cannot defend these decisions because I am not a member of that faith nor do I believe that it has a proper interpretation of the Bible. The issue is clearly legal. The mood of the time is not to involve yourself against the will of a patient even though it is clearly for the patient's benefit.

Greifer: What you are saying is, "it is going to be." But an individual still has a moral and ethical obligation. Should we forget the law? Should a doctor go to the law? Should he use the court system and do everything possible to get the results he wishes even though, as you pointed out, the court may already have decided against it?

Tendler: Surely the obligation to save a life includes the discomfort of going to court to sign documents in the hope of saving the patient's life.

The Family Part in Decisions

Question: Is it fair, at the bedside, to let the family decide? Is it fair for the husband to decide about his wife with carcinoma? Talking about the integration of the physician, the ethicist, the social worker, is it fair to then leave the decision to the husband or the family? Can the family always be right?

Greifer: If a hospital has a committee on medical ethics to determine whether support systems or treatment should be given or withheld from a patient, fine. The family or the committee can only respond to the physician who gives them the information. This is true at the bedside. The family can only respond within the attitude or atmosphere, within the intelligence given to them by the physician. Much of their interpretation will be directly related in many ways to the doctor's opinion to begin with. This has always been a question: Is there such a thing as a fully informed individual? What really counts is how the physician talks to the family. In certain areas of this country, 75%–80% of families will donate a kidney. In other parts of the United States, less than 20% will. I don't think the people are kinder in Iowa than in New York. I think it is basically the approach of the physician, the information he or she gives.

Rosner: The decision-making process is a difficult question. The family should not be the deciding factor. Consider the problem with abortion. If you ask anyone on the street who should make the decision about whether a woman should have an abortion or not, the answer 99 times out of 100 will be, the woman, it's her body. This is fallacious thinking. Obviously, in Judaism, it is not her body. It is God's body that is given to her on loan. Maybe somebody other than the woman should make the decision or do so jointly with the woman. What about the husband or the boyfriend in an unmarried situation? What about the rabbi, or society, or the doctor or siblings? Maybe we should ask them. It is a multifaceted, multifactorial problem.

The same is true about whether to treat a terminally ill patient. Neither the doctor, nor the family, nor the rabbi, nor society should make the decision alone. It has got to be the team approach as we know it in medicine. We have a team of physicians, psychologists, social workers, and nurses taking care of the medical needs of the patient. The psychosocial, ethical, and religious and spiritual needs of the patient also require a team. The doctor may be the leader, the captain of the ship. But the decision must be made jointly. All the people involved must put the facts on the table so an intelligent and reasonable decision can be reached based on all the ethical principles that are brought up.

Gribetz: A husband and a wife, or a family, should discuss beforehand how they want to be treated. Those wishes should be respected. It is a matter of communication in families. For want of better guidelines, I can't see who else would make the decision for a terminally ill patient than the family members who have been with the person for years. It is not a physician's decision. Nor would I leave it up to a rabbi. I would ask his advice, but I wouldn't give him the responsibility of making the decision. Certainly the doctor should not. It comes down to the point that they will ask the doctor, What would you do if this were your mother, if this were your father? Again, the doctor is free to reply and the rabbi may feel free to reply. But it is an individual decision. This is the way society exists now. What it will be like in the future I don't know.

The Rabbi's Part in Decisions

Question: What is the role of the rabbi in the decision-making process?

Tendler: Two circumstances invoke decisions on when not to treat. Sometimes a rabbi is asked by a member of the faith and the answer they want is both helpful and supportive. It is helpful in decision-making and immensely supportive because any guilt feelings are eradicated. For example, the patient is an Orthodox Jew, comes from an Orthodox family, and has completely lived his life by the rules of the Orthodox Jew. Can I disengage the oxygen pipe from his mask so that he can die sooner than he would die otherwise? We have a clear answer—no, don't do it. When the issue involves initiating new therapies, sometimes we see no need to introduce a new treatment modality. If the patient's lifestyle leads him or her to consult a rabbi for important decisions, the family needs the psychological support of such rabbinic decisions. Very often you get questions that do not need an answer. People of other faiths want to bounce something off your back, throw the ball against the wall and see what happens. They're sending up confused signals. They want to hear another opinion, but not a directive.

You can see the full scope of a decision-making process, the real decision-making being done by society. What the family wants to know is how does the doctor view it, how does the rabbi view it. They are under such emotional stress that they are in a bind; tension almost immobilizes their decision making. The stand of biblical ethics is sometimes the single most helpful bit of advice a family receives. Although legally the family makes the decision, practically it is usually the physician and the clergy who direct the decision. There is another dimension to the whole problem. The family ought to be considered first. The family members are the people who share the burdens. The family will observe the mourning rites. The family pays the bills. The family is very much involved, yet there can be great problems if the family is to be consulted alone.

"Imminent Breakthrough" Decisions

Question: One of the best reasons for keeping a patient alive as long as possible is the possibility, however remote, of the appearance of a specific treatment, such as insulin for diabetes, vitamin B-12 for pernicious anemia, or penicillin for pneumonia. That a cure may be here tomorrow is always in mind. In all these things, you've got to be what we call a smart doctor. You've got to know what's available. For example, if a patient has intractable angina, you don't want to write him off without the consideration of coronary bypass surgery. It is the medical knowledge which has to be made available. How much "imminent break-through" medicine should a physician practice?

Tendler: That we are bound by natural law is one of the most difficult concepts to sell a patient. It is easier to sell it to a physician. We have to deal with the facts as they are in making ethical decisions. The response from the ethical point of view is that if God is prepared to reveal new secrets of nature for the benefit of us all, he surely will do so in time to save this patient. Therefore, the idea that you have to undertake an unethical or unacceptable act, such as risky surgery, so that the patient will stay alive long enough to get a new cure which is in the offing, is wishful thinking that doesn't lend itself to honest ethical decisions. It, nevertheless, is significant from the patient's vantagepoint. Any patient who wants to see another doctor, surely can. Another doctor may have the "secret." The patient goes to Germany because somebody in a clinic hidden away on a mountaintop has a secret that no one else has. Hope springs eternal. But hope cannot be a factor in ethical decision-making.

Battery-Operated Machinery

Question: If it is unethical to turn off life-supporting machines, as in the Quinlan case, may battery-operated machinery be substituted and allowed to operate during the period of battery viability without replacing the batteries?

Tendler: Actually, that's a valid question, although it doesn't sound good at first. Analyze it. Is there a difference between discontinuing a treatment and not initiating a new treatment? That is really what the question is. When a fellow is plugged into Con Edison and the pump is working all the time, you have to pull the plug. When he is on a battery and the battery runs out, do you replace the battery? Is this patient subject to further treatment? A decision has to be made every time the battery needs charging. In an ethical system based upon talmudic logic, it is a valid question. The key point to address is sensitivity to the issue. If the patient warrants treatment, he or she warrants initiation of treatment. Treatment must be kept up regardless of the cost per diem, as in the Quinlan case, a tragedy of life in which the quality of life is not the ethical import.

If, however, you are dealing with inflating the balloons which replace the lungs and the patient is brain-dead, you are questioning whether you should discontinue or not. It makes no difference whether it is the time to replace the battery or time to pull the plug. Both fall into the same category. The decision, however, to institute treatment may be entirely different from the decision to continue treatment. The key issue is the issue of intent.

Talmudic View of Pain

Question: Give some bases and sources from the Talmud or Bible for the unacceptability of pain. Are there not the elements coincidental with the proper utility of pain? Can you use pain as the decision point in decision-making?

Tendler: The source is a discussion of Rabbi ben Tradyon (Talmud, Tractate Avoda Zara, 18a). It is a decision to discontinue treatment. In the example, the treatment was lowering the temperature of protein denaturation due to the fire that surrounded the dying martyr. The wet wool placed on his heart was intended as a cure for the disease of excessive heat. The decision there is solely based upon pain. That is one of the prime sources from the Talmud. There is also the one concerning the death of Rabbi Juda the Prince; he was dying in agony and his students were offering him the most effective cure available, prayer. The maidservant saw fit to go up on the roof and toss down a bucket of water, which interrupted the prayer service and thus allowed her master to die. The rabbis commended the maidservant for the wisdom of her act, indicating that the agony of death is sufficient reason to withhold further treatment (Talmud, Tractate Ketuboth, 104).

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III. End of Life

Definition of Death and Dying

BERNARD KABAKOW, M.D.

The medical approach to death and dying can be illuminated by the story of a patient I cared for several years ago. He was a 55-year-old man who entered the hospital emergency room in shock and cardiac arrest after acute myocardial infarction. Following defibrillation, intubation, and the use of vasopressors, his rhythm changed from ventricular fibrillation to regular sinus and his blood pressure became normal. Eventually, he was weaned from vasopressors. A tracheotomy was performed on the fourth hospital day. He had spontaneous respirations and normal cardiac function, but he never regained consciousness. An electroencephalogram showed bilateral diffuse abnormality. During the ensuing ten months, he had several episodes of pneumonia and sepsis, each successfully treated with antibiotics. The tracheotomy required frequent suctioning. His body weight declined from 140 lb on admission to an estimated 80 lb, and he had several decubiti. He was fed by stomach tube and had an indwelling urinary catheter. On hospital day 220 he developed another episode of pneumonia and sepsis. At this point, the family approached me and the house staff, explaining that they felt there was no point in trying to keep the patient alive any longer by using antibiotics to treat his pneumonia. They felt he would never recover brain function, and the quality of his life was not worth sustaining. The physicians complied with the family's wishes and the patient died on hospital day 224.

In the past several years, we have begun to think about such decisions. The American philosopher Max Block once wrote an essay, "Think Only as a Last Resort," in which he maintained that it was often better for mental health to make an impulsive decision than to think a problem over excessively and at length. The fact remains, however, that we have begun to think about and agonize over our decisions. The questions that arise are really basic. Who has the right to make the decision about life and death—the family, the patient, the doctor, the courts? As a corollary, what rights does the comatose patient have? Is there any freedom of choice in such matters if we believe that God, who has created life, should be the one to take it away? The Medical Ethics Committee of the Federation of Jewish Philanthropies, of which I am a member, has discussed these questions at length, and I want to indicate the sense I have of how most physicians approach such problems.

The case I have described illustrates the problem of coma without brain death in which no active measures are used to hasten death but in which a specific complication, in this case pneumonia, is not treated and—because of our neglect or passivity—the patient dies. We physicians could not say for certain how long the patient had to live. Such patients have been known to linger on for years in a coma, but a person who has remained comatose for so long after cardiac arrest rarely recovers brain function. The ethical problem is that these patients do not have a finite life expectancy, whereas the cancer patient, or patients with true brain death, as I define it, are expected to die in the very near future and the decision not to treat is a much easier one. Many variations have to be dealt with; for example, prolonged bowel obstruction requiring surgery for relief, or upper gastrointestinal bleeding requiring many blood transfusions in a hospital with a shortage of blood in the blood bank. At Medical Ethics Committee meetings I have found the long discussions about how to manage these complications interesting but much removed from the

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bedside, where a physician is most comfortable. There was no possibility of this patient waking up and becoming a functioning human being. I was also dealing with a family that was psychologically and financially broken by the tragedy. At the onset of his illness the patient's wife and children visited him daily for many hours at a time and talked only of his living. After ten months, they visited him only about twice a week and thought and talked only about his dying. They were financially secure at the onset of his illness; after ten months, they had used up all their savings and were on welfare.

Rabbis and ethicists say that psychological and financial factors should have no relevance to decisions on life and death. In theory, they are probably right; but those of us who are involved with the day-to-day care of patients cannot help but be concerned with and involved in the future lives of our patients' survivors. We are very much concerned that the bereaved carry on their lives with a minimal burden of guilt and despair and with some sort of secure hold on the future.

Definition of Brain Death at Beth Israel. To turn to the increasingly important definition of brain death: until recently it was accepted that when respirations and heart action stopped, the brain would die in a matter of minutes, so that the obvious criteria, no heart beat and no breathing, were accepted as synonymous with death. But modern resuscitative and supportive measures now allow us to restore "life" as judged by the ancient medical standards of persistent respiration and continued heart beat, and these functions can be maintained indefinitely even when there is not the remotest possibility of recovery of consciousness following massive or irreversible brain damage. It has become necessary, therefore, to establish clear-cut criteria of brain death. In 1971-1972, the National Institutes of Health undertook a study to define these criteria. This study has been refined in the so-called Harvard criteria (1).

At Beth Israel Medical Center, we have adopted specific criteria for the diagnosis of brain death (2), following the completion of any indicated diagnostic procedures to establish the cause of the comatose condition and following the institution of indicated therapeutic efforts. Two examinations by neurologists or neurosurgeons are required to verify brain death, the second examination taking place twelve hours after the first. If the criteria for brain death are found to exist on both examinations and no contrary findings are reported in the intervening time, after the second clinical examination, an electroencephalogram is used to evaluate brain-wave activity.

If the EEG tracing is officially interpreted as iso-electric by a designated electroencephalographer, the patient is pronounced dead. Support systems are discontinued unless permission is given for organ transplantation. Support can be continued when the family cannot be reached to discuss permission for organ donation.

At Beth Israel, examinations to fulfill the criteria of brain death are as follows.

1. Any clinical suspicion that the comatose state is caused by reversible drug effect should be followed up and ruled out. Adequate time should be allowed for screening for drugs that can simulate brain death. Routine screening at Beth Israel Medical Center is for cocaine, metabolite, barbiturates, amphetamine, codeine, morphine, methadone, methamphetamine, phenytoin, benzodiazepine, propoxyphene, amitriptyline, phenothiazines, phencyclidine, ethchlorvynol (Placidyl).
2. Body temperature 95°F or less.
3. Unresponsive coma: no spontaneous movements and no response to noxious stimuli.
4. Absent pupillary response to light.
5. Absent eye movements in response to head turning (oculocephalic response); if absent, ice-water caloric testing should be done.
6. Absent corneal reflexes.
7. Ventilation with pure oxygen or an oxygen and carbon dioxide mixture for ten minutes before withdrawal of the ventilator, followed by passive flow of oxygen. This procedure allows $P_A\ CO_2$ to rise without hazardous hypoxia. Hypercarbia adequately stimulates respiratory effort within 30 seconds when $P_A\ CO_2$ is greater than 60 mm Hg. A ten-minute period of apnea is usually sufficient to attain this level of hypercarbia. Arterial blood gas testing can confirm this level.

In suport of these criteria, 2,650 patients were surveyed nationally by isoelectric encephalogram. Only three of these patients recovered, and all were cases of drug overdosage (3). More recently (4), a technique using radioisotope angiography has been employed at the bedside to further differentiate true brain death from other causes of profound coma. The vital importance of a legally accepted definition of brain death lies in the matter of organ transplantation. I feel that physicians must have some sort of legislation to define death similar to the definition at Beth Israel so that there will be no legal complications.

Laws on Withdrawing Life Supports. Several states have enacted, or are considering, laws providing that an adult, in a signed and witnessed document, may direct his or her physician to withhold or withdraw life support systems in the event of a terminal condition when death becomes imminent. Supporters of such legislation feel that, in the interest of protecting individual autonomy, prolongation of life for persons with a terminal condition may cause loss of patient dignity and unnecessary pain and suffering while providing nothing medically necessary or beneficial to the patient.

The Federation's Medical Ethics Committee, along with many individual physicians and ethicists, opposes this type of legislation for many reasons. It would, we feel, interfere with the time-honored relationship between patient and family and doctor. It would replace the physician's judgment with legislation applicable to general situations but often without application to an individual patient. The language of the California Natural Death Act is vague and ambiguous and could result in long and costly proceedings leading to court-made decisions that may not be in the best interest of the patient.

The reason for our opposing such a law is that good medical treatment can often control unnecessary pain and relieve suffering. Two former residents associated with Dr. Maurice Strauss, formerly chief of medicine at the Veterans Administration Hospital in Boston, have related how he handled his pain while in the terminal stages of esophageal cancer. By receiving morphine every four hours, he was able to prevent pain that had previously been intolerable. At the same time, he remained in control of his faculties (5). He never became addicted to morphine. Workers in the hospice movement and elsewhere (6) have had similar experiences.

Other reasons for our opposing such laws are that, first, diseases untreatable today may become treatable tomorrow. Subacute bacterial endocarditis was invariably fatal in 1941; a short time after the discovery of penicillin, it became curable. Second, a mental state may occur in which the patient requests death and is not given suitable alternatives or options. And third, the diagnosis may be wrong.

Illustrative Case Histories. A 33-year-old woman had a mastectomy. At age 36, she had jaundice, hepatomegaly, cold areas on liver scan, abdominal and pelvic masses, and lytic bone metastases. The physician believed that the outlook was poor. She was thought to have less than a year to live and her husband was told to make provisions for the children. The husband pleaded: "Doctor, try anything." Successive remissions occurred with the use of male hormone, oophorectomy, adrenalectomy, chemotherapy, and radiation. She died five years later, after four relatively good years, free of the ravages of her disease.

A 42-year-old woman entered the hospital with severe shortness of breath. She had had a mastectomy two years before. Chest x-ray showed a massive left pleural effusion and an enlarged heart. Malignant cells were found in the pleural and pericardial fluid and a radiation castration was done without any benefit. A liver scan was positive for metastases. Chemotherapy brought some improvement, but she then developed pericardial tamponade. In an emergency operation a pericardial window was created. She resumed chemotherapy, did well for several weeks, and then had a cardiorespiratory arrest. She was successfully resuscitated and placed in the intensive care unit. The housestaff at that time did not think that she should be resuscitated in the event of another arrest. They argued that she had preterminal cancer with pleural, pericardial, and liver metastases and that resuscitative efforts should not be made on such a patient. The attending physician disagreed and asked the husband to agree to resuscitation should arrest occur. That night the patient arrested several times, was resuscitated, and finally died. The cause of death was a massive pulmonary embolism, and the autopsy showed that this was indeed the cause of death and that metastases were minimal. The liver scan had been a false-positive one. The patient did not die of cancer but died of an unrelated disease.

Classification Attempts. One of the attempts to classify critically ill patients in terms of what therapeutic measures should be expended in their care (7) is as follows.

Category I: maximum therapeutic effort without reservation. Examples would be a patient who is admitted to the cardiac care unit with a myocardial infarction or an otherwise healthy patient with massive gastrointestinal bleeding.

Category II: maximum therapeutic effort without reservation for a given period. For example, for a patient with a malignancy who has developed hemorrhage or sepsis, the decision may be to give maximum therapeutic effort for 24–48 hours. If treatment succeeds, the patient has been restored to his or her previous state.

Category III: no active or specific therapy to be initiated.

Category IV: true brain death. All therapy will be stopped and all supportive systems will be discontinued.

The difficulties arise when a terminal patient classified in category III, for example, is admitted to the general medical floor of a hospital. The patient is certain to die within a short, but undefinable, period. The family finds they can no longer care for the patient at home and the attending physician arranges for the hospital bed. The housestaff examine the patient and begin to treat actively—intravenous therapy for dehydration; restoration of the patient's electrolytes to normal; for severe anemia, blood is given; for bleeding from the stomach, a stomach tube is inserted. The family is often incensed. They want nothing to be done. The attending physician is often ambivalent because he wants to satisfy the family but he must have some justification for admitting the patient. The young intern, fresh from the medical school teaching that for every disease there is a treatment, is eager to treat the patient. Lack of communication between family, physician, housestaff, and nurse makes for a distasteful situation.

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Rabbinic Comment: Definition of Death and Dying

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Representing the Medical Ethics Committee, I can offer the principles of rabbinic thinking for physicians to consider when faced with the question of brain death or the definition of death.

The history of the definition of death begins in the Talmud in an unlikely context, the context of sabbath observance. The relevant mishnah is not primarily concerned with death, but with proper sabbath observance. It tells what to do if debris has fallen upon a person on the sabbath: *bodekin ad hahotem,* remove enough debris until you uncover the nostrils. With the nostrils exposed, you can ascertain whether the victim is still breathing. The duty to save life overrides all prohibitions of work on the sabbath; otherwise removing fallen debris would be a violation of the sabbath. If the victim is already dead, you may as well leave the body as is until sundown, then minister to the dead person.

On the basis of this mishnah and discussions of it in the Talmud, death is defined as the cessation of respiration as ascertained at the nostrils. There is another opinion in the Talmud, namely, that inspection should continue up to the heart. Rabbi Aaron Soloveichik, in an article on the definition of death, refers to this point of view and cites the philosophers of the Middle Ages who point to biblical verses in which life is equated with the heart. True, the Bible does say *vayippah b'appav nishmat hayyim,* "and he breathed into his nostrils the breath of life." The creation narrative makes breath the sign of life. But the Bible also says, "Love the Lord thy God with all thy heart and with all thy soul." "With all thy heart" may be another way of saying "with all thy life," so you do have a choice.

However, what happens if something like brain death occurs while respiration and heart activity seem to be continuing? The question has occupied the rabbis in recent years. A 37-page article in *Noam,* an annual halakhic journal, by Rabbi A. Steinberg, a disciple of Tzitz Eliezer, Rabbi Eliezer Waldenberg, argues against brain death. His reason is the vagueness and multiplicity of the kinds of brain death. To him, even the Harvard criteria are really not tests of brain death but of brain dysfunction. Our committee, agreeing with Rabbi Tendler's views and his representation of the view of Rabbi Feinstein, has accepted total cessation of brain function—including that of brain stem—as death. This cellular destruction presumes interference with circulation to the medulla and can be equated in Jewish law with decapitation. We believe, with Rabbi Unterman and others, that successfully performing a heart transplant is a *mitzvah,* "good deed," because it saves a life—and you cannot do so unless you accept this definitive destruction of brain and brain stem function as death.

The Uniform Anatomical Gift Act passed by 50 states requires two transplant teams, one to minister to the donee and a different team to take the heart from the donor. Otherwise, you have a conflict of interest. Physicians can be so anxious to give the heart to the donee that they might be

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unconsciously prejudiced in determining whether the donor is actually dead.

At the same time, extreme caution in determining that death has occurred may seem more pious but may in fact be less pious. Paul Ramsey, in another context, says we may sometimes be guilty of breathing life into an unburied corpse. That is a vivid phrase. It's not wise or moral to keep alive an unburied corpse, certainly not from a halakhic standpoint. As the authoritative Hatam Sofer said a century ago, one must avoid being too *machmir* (cautious) about whether the indicia of death are yet present, to avoid being guilty of *halanat ha-met,* desecrating the body by delaying burial. So both for transplants and nondesecration of the body, it is important to accept whatever technologic criteria can be valid in Jewish law.

It remains true, nonetheless, that if you are not cautious enough, you can be guilty of murder. To hasten death by an instant is to be guilty of murder. Another text in the Talmud tells us what to do when a person does expire. There is a procedure. You close the eyes, you fold up the hands, you bring the feet together. The Mishnah says, unless you are absolutely sure of death, *ein m'atzmin et ha-einayim,* you can't close the eyes or fold the hands or do anything else. Although the person may be near death, if by touching him unduly you hasten death by a second, you are guilty of murder. Murder means taking a person's life, even a small part of it. The Talmud picturesquely compares life to a candle. A candle is flickering, but still aglow. If you touch the candle, you cause the flame to expire. It was flickering, but your touch extinguished the flame. Similarly, by touching, you can hasten a person's death, even by a moment. All this places us on a tightrope between being too cautious and being cautious enough.

Practically speaking, what do you do in a situation as described by Dr. Kabakow? When, by withholding treatment indicated in a terminally ill patient or one in extreme pain, are you hastening death? Some guidance is available from a line of legal-moral provisions that begins with the Talmud. But first, let me cite a later source, a thirteenth-century text called *Sefer Hasidim,* which tells of certain situations in which a person is dying but there is an artificial impediment to the death process. The cases are rather bizarre, apparently unrelated to our experiences. Two kinds of artificial impediments are described: if someone is chopping wood outside the room of a dying person, and the rhythm of the noise is keeping the soul from departing, or if there is salt on his tongue and the tartness of the salt focuses his mind and keeps him from dying, it is allowable to remove these impediments to what would otherwise be the natural death process. These quaint examples aside, the principle is codified by Rabbi Moses Isserles in his sixteenth-century work. One may *me-sir ha-monea,* "remove the impediment." Of course, it is for us now to determine what an impediment is; it can't be intravenous feeding or oxygen.

Some later halakhic authorities say removing artificial impediments is a *mitzvah,* a "good deed," not just permissible. The story in the Talmud has to do with the martyrdom of Rabbi Hanina ben Tradyon, in the context of the martyrdom of other great rabbis in the Hadrianic persecutions in ancient Rome. Their crime was that they violated the Roman ban against teaching the Torah. They defied the ban because, they said, if we don't teach the Torah we're as good as dead anyway—the Torah is "our life and the length of our days." The rabbis were put to death painfully. The martyrdom of ben Tradyon was particularly gruesome. The Romans subjected him to a slow death by fire, even placing moistened wool around his heart to delay death and prolong the agony.

(The word "euthanasia," coined by Sir Thomas More, is a literal translation of the Hebrew phrase *mitah yafah.* The source of the phrase in the Talmud is the statement by Rabbi Akiva, most noted of the Hadrianic martyrs, who had taught that even a convicted criminal who must be put to death for a crime should be given a narcotic to be spared the pain of the execution. The Bible says, "Love thy neighbor as thyself." This means, Rabbi Akiva taught, give a *mitah yafah,* a euthanasia, because love of neighbor means to spare that pain even to the person who must be executed.)

The Talmud goes on to relate that the pupils of Rabbi Hanina ben Tradyon, beholding the tragic and terrifying scene of his agony, tried to help him. They said, "Rabbi, why don't you open your mouth so the smoke from the flames might suffocate you; you'll die more quickly and with less pain." But he answered courageously that he would then be hastening his own death, whereas only God can take life. His executioner took pity on Rabbi Hanina and offered to remove the pads of wool from around his heart. To this Rabbi Hanina assented. The moistened wool was removed and Rabbi Hanina died. The Talmud declares that Rabbi Hanina and the executioner both went straight to Heaven, which made another rabbi reflect when he heard of it. He said, "The rest of us spend our lives doing good deeds to earn a share in Heaven, while that executioner earned his portion in paradise by just one great act of kindness." For, says the Talmud, some can acquire their portion in one moment, *yesh koneh olamo b'sha-ah ahat.* This implies that what the executioner did was meritorious. So what we derive from this talmudic story is that, whereas you cannot hasten death by such means as by opening your mouth to allow the smoke to come into your lungs, you can remove an artificial impediment, such as the balls of wool which were artificially placed there. You certainly can remove an artificial impediment—that is a meritorious act.

This, then, gives us a kind of guideline for how we can proceed in defining death. It also helps define the role of the consulting rabbi in questions of medical ethics. The rabbi brings to bear halakhic guidelines and prescriptions and helps the physician in the joint quest for the ethical resolution of dilemmas. At times, the rabbi is the disinterested statesman helping to provide long-range insights to the subjective politician. Just as you need a statesman along with a politician, or an expert in strategy as well as tactics, you need someone who's going to consider the long view, who will air otherwise self-evident moral principles in the face of daily pressures, or even compassionate but subjective desires.

The moral sense is the preciousness of life. It comes from many teachings in the Talmud. In my magnum opus on birth control and abortion, I point out that Jewish law on abortion is both very liberal and very illiberal. It is liberal in the sense that, for the entire span of gestation, the Mishnah provides that if the woman is in difficult childbirth, one can dismember the fetus limb by limb, if necessary, to save her life or health, even, that is, up to the moment of birth.

If the mother and child are locked in mortal combat—extravagant phrase—then, says the Mishnah, you not only may, you must dismember the fetus, because the fetus is potential life and actual life takes precedence over potential life. That is a very liberal principle—though it seems too liberal because people may take advantage of it wrongly for abortion on demand. Nevertheless, the principle remains: do not give precedence to potential life over actual life.

On the other hand, the Mishnah continues, if the birth process has begun, if the head has emerged or, in the case of a breech birth, if half of the child has emerged, then *ein nog'in bo,* then you can't touch it; you can't harm that fetus anymore because *ein dohin nefesh mip'nei nefesh,* you can't set aside one life for another.

This ruling is very illiberal. What it says is that this mother, with presumably a husband and other children dependent upon her, who has her various associations in life, is yet only equal to this newborn babe with no affiliations or relationships. No one yet depends on this baby, it has no responsibilities to meet. Yet the Mishnah teaches that life is life; that the mother's life is not more precious than the baby's. In other words, distinctions based on quality of life are inadmissible. When two actual lives are involved, no concept of quality of life can be brought to bear, only the concept of sanctity of life, which is absolute; you can't touch it. This is an important principle; we too often lose sight of sanctity vs. quality of life.

I remember visiting a patient in New York University Hospital who told me that I had missed the excitement in the hospital the night before. She said, "We have an airway unit in the hospital." What, I asked, is an airway unit? "It's a unit which serves to relieve congestion; to remove obstruction to breathing. This unit," she said, "is staffed 24 hours a day; if a patient has difficulty in the middle of the night and can't breathe, then an alarm is sounded and the airway team rushes in with the airway unit and helps relieve the breathing." This was the second night in a row the airway team was called into service and two or three of the interns were grumbling about it, saying, "Imagine bothering us for the obstructed breathing of a 90-year-old woman." The chief resident overheard the complaining and called them together for a reprimand. "How dare you," he said. "How dare you say 'only' a 90-year-old woman. That's a wholly wrong assumption and a wrong moral stance toward life. Do you believe that because the woman is 90 she is less worth saving than a woman 19 or a girl of 9?" Life is precious at whatever age, regardless of prospects, productivity, or considerations of quality of life.

For similar reasons, our Medical Ethics Committee was opposed to the idea of a living will. We opposed it because the living will nourishes the attitude that "life" is to be determined by its productivity, not by its absolute sanctity. The attitude that life is only worth protecting or preserving if it is productive or young and promising flies in the face of all spiritual concepts of the Jewish tradition. From the Jewish spiritual standpoint, the older a person is, the more precious that life may be, because life is the soul and the soul is the *n'shamah,* really the accumulation of experiences, learning, memories, relationships. All these are part of the cumulative content of the soul; more is accumulated as life progresses. Perhaps the older a person is, the more precious.

I learned a similar lesson in my younger, more presumptuous days. In my congregation was a terminally ill man in great pain from cancer. His wife related that she had the choice, at one point, of allowing treatment to cease so that her husband could die and be relieved of his pain, or of allowing continued treatment, which at best could only enable her husband to live another six months, with pain. She decided to allow continued treatment, figuring there might be some miracle cure or a remission during that period. Six months later, the man died, without this relief. Visiting her during the mourning period, I asked her if, having to choose again, she would still make the same choice, knowing what she did—that his life was prolonged in pain, there was no miracle. She said yes. I, being brash and young, asked her why. She said, "I'll tell you, young man. During these six months, my husband was indeed in pain. But despite the pain, in these same six months, he witnessed the birth of one more grandchild and the marriage of one more daughter. I can tell you without doubt that the exquisite pleasure he took in such family events pierced the veil, transcended the pain, and gave his life profound satisfaction. The pleasure of these family occasions was so great as to triumph over the pain that we seemed to be so worried about. Life is life and larger than pain."

That taught me something important and helped me appreciate the Jewish spiritual attitude to life and to pain. Pain is something we're all very much concerned to avoid. The pain of dumb animals, and even more the pain of human beings, is to be avoided, to be prevented, to be relieved. But that doesn't mean we're prepared to hasten death in the name of relief from pain. We pray that science and medical knowledge can advance further to help us relieve pain, but life in pain is still more precious than no life. We need to revere it more, despite our ongoing concern to make it more bearable.

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Autopsy

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The history of the development of the autopsy, as an integral part of medical practice, is glorious. The autopsy grew from the desire of physicians to understand the natural history of disease, from the interest of physicians to establish sound criteria for making accurate diagnoses, and from the determination of physicians to provide reason and judgment in place of ignorance and guesswork. The evolution of the autopsy as the major element in deciphering the mysteries of disease was neither direct nor simple, only inevitable, for the autopsy had its birth in the curiosity of generations of physicians unwilling to accept the darkness and the errors of either the past or their own times. The birth process took centuries, and medicine has been ennobled by those who have been permitted to peer beneath the protective body covers to reveal, recognize, and comprehend why and how human beings suffer from disease. The slow and tortuous path in the fabrication of a rational analysis of sickness was impeded for more than three thousand years by ignorance, by fear, and by superstition.

Although autopsies were performed more than 2,000 years before the common era in Egypt and 1,000 years before the common era in India, it was Galen, in Roman times, who provided the first systematic and sound basis for correlating structure and function in disease. Human dissection, however, was forbidden, and Galen's knowledge and understanding came mostly from the study of apes and pigs. Galen's teachings in medicine, based mostly on animal studies, was to be the dominant influence for thirteen centuries until Vesalius, in 1543, championed the dissection of human bodies as the only means to understand the physical nature of human beings. It was not until 1758, 215 years later, that dissections became an integral part of education in the medical school in Vienna.

In spite of this progress, the practice of medicine was only a train of obscure and incoherent phenomena. In his seventy-ninth year, Giovanni Battista Morgagni committed to posterity his lifetime of study, contemplation, and analysis. Morgagni, for the first time, integrated the complaints of the patient with the physical manifestations of the disease during life and interpreted them in the shining light of his findings at autopsy. It is two centuries since Morgagni flung open the twin doors of inquiry and reason, and it is no exaggeration to state that the entire edifice of medical practice rests most securely on the practice of clinical observation and postmortem dissection established by Morgagni and augmented by his spiritual descendants, Bichat and Laennec in Paris, Hodgkin in London, Rokitansky in Vienna, Virchow in Berlin, and Paul Klemperer at The Mount Sinai Hospital in New York. They have taught us that the single most effective way to uncover the obscurities of disease is to perform the autopsy. The inscription on the wall of our autopsy room at The Mount Sinai Hospital reads *hic locus est ubi mors gaudet succerere vitae,* "this place is where death rejoices in giving to the living." The entire history of the autopsy, which is presented here in a most superficial way, is summarized in that inscription. The Hebrew toast *L'Chaim,* "to life," also expresses the reason for performing autopsies. All the diseases that have been understood mostly by evaluation of the autopsy could not be discussed even in a month-long seminar. Indeed, it would take hours just to catalog the conditions that have become well understood in the last 25 years because of the autopsy.

Contributions to Society

The autopsy contributes much to society: First, perhaps, are tissues for tranplantation, which I

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discuss in a section below. Second, pharmacological extracts; a variety of pharmacologically active, therapeutically useful, natural substances can be obtained only at autopsy. One example is human growth hormone used for the correction of major growth impairment in childhood. This is obtainable only from human pituitary glands recovered at autopsy. Third, autopsy could well serve us better in compiling vital statistics. The vital statistics that determine health and governmental policies are imprecise. At our superb institution, death certificates—which should include both the direct cause of death and the contributing illnesses—are incorrect in more than 50% of the cases. Fourth, autopsy can be used in charting the epidemiology of environmental pathology, in light of the innumerable influences our environment may have on us. Are animal experiments enough to fully understand the effects of the environment on humans? Mice are not men. Will deleterious effects be recognized only when disease is obvious? The large-scale analysis of the population at autopsy could provide for the recognition of the early effects of environment-induced injury, but, of course, we do not have a national program for large-scale autopsy evaluation of the population. Not only would we have the potential for better understanding the new diseases of our times, but broad application of the autopsy would enable us to find clues about other scourges of mankind by identifying precursor lesions. The autopsy of the patient with noncancerous disease, such as heart or kidney disease, could potentially provide invaluable information about the earliest changes of cancer at the stage before it is clinically obvious and easily recognized. The more we see, the more we know. Autopsy could also be useful in maintaining the quality of medical care.

The contributions of the autopsy to law enforcement are many and well-known, encompassing forensic pathology, where it is useful in violent deaths, toxicology, child abuse, and the protection of the innocent, and also encompassing worker's compensation claims.

However, contributions of the autopsy to medical education are not completely recognized. The effective preparation of the pathologist-in-training, the physician who must evaluate and interpret changes in tissues removed from living patients, can only be achieved by his or her first mastering the autopsy. Moreover, this is the age of continuing medical education for the physician. I challenge any physician to demonstrate a more reliable, more effective, more vivid learning experience than the lesson that can only be obtained by following a patient during life and then studying that patient after death. This is still the most direct path to excellence in medical practice, for medical students, for nurses, for paraprofessionals.

The autopsy also contributes to biomedical research by aiding in determining the causes of disease; evaluating treatment efficacy and toxicity; finding applications of new methods; and recovery of materials in biochemical and microbiologic studies. This listing can only skim the surface. Above all, the autopsy allows us to understand disease and to understand what we as physicians accomplish in our attempts to treat disease.

The autopsy contributes to the family, for instance by contributing to education about familial diseases and the prevention and treatment of communicable diseases. The autopsy provides for the living in some abstract ways, but also in very concrete senses—for one thing, it is essential in confirming insurance benefits. And although a confident discussion of the phenomenon of guilt that follows virtually every death is beyond my ability, I do note that it may take years for surviving family members to resolve their guilt. An understanding of the nature of the disease, the effects of therapy, and the basis of death may be of inestimatable value in removing this burden. This has been well documented in cases of what is called "sudden infant death syndrome"; at some medical centers, the pathologist has been an integral part of the team working with the parents after the death of the infant. The performance of the autopsy is only the first step in this regard and can only be useful if it is effectively utilized by interested members of the healthcare team, as well as by a concerned and committed clergy.

Contributions of the autopsy to clinicians are well established: (a) evaluation of accuracy of diagnostic modalities; (b) evaluation of quality of surgical procedures; (c) evaluation of the efficacy and toxicity of therapy; (d) confirmation, clarification, and correction of diagnoses; (e) determination of cause of death and its relevance to major disease process. The autopsy is the final and most consistent guide for the perplexed physician. The autopsy dissipates doubt. The autopsy is the only yardstick of the effectiveness of the physician's activities in the patient who dies. No other means of evaluation provides answers; only guesses.

The autopsy contributes to the hospital itself. The institutions that care for the sick and dying need the autopsy. Mount Sinai needs the autopsy. The autopsy is the guarantor of excellence. The hospital that does not use the autopsy fully, that does not exploit the autopsy to insure the quality of medical care by confirming the accuracy of diagnoses and the relevance of therapy and detecting inappropriate or injurious treatment pays only lip service to the concept of excellence. Reliability of diagnoses has been evaluated in a number of major institutions in the United States and Europe in the past several years. Autopsy uncovers clinically significant phenomena in 50% of the cases. Moreover, in as many as one in five cases, the autopsy provides the correct diagnosis of the disease.

The autopsy is a vital, indispensable component in assessing the medical care of patients who have died. Without the autopsy, there can be no certainty about diagnoses, no efffective evaluation of therapy, and no guarantee of the quality of practice.

The Jewish View

Some 30 years ago the Sephardic chief rabbi, Ben Zion Ouziel, provided learned testimony for the view that autopsies are of inestimable value and that there is no proscription, as far as the living are concerned, against the autopsy:

> Anyone with a knowledge of the development and progress of medicine will not for a moment doubt the benefits which accrue from autopsies and dissections. Autopsies are of inestimable value in establishing the cause of the ailment and its effect upon other organs of the body. In addition, where the preservation of life and the interests of the living are concerned, there is neither *nivvul ha-met*, nor desecration of the body.

The Babylonian Talmud comments on the usefulness of certain animal livers for predicting the future. Zones of the liver were thought to represent such things as the harvest, the weather, or other events that could affect society.

Less well known is the evidence in the Talmud that suggests that human dissections of various kinds were performed in antiquity (Table 1). Rabbi Yishmael commented on the autopsies performed on Cleopatra's slaves. Even more directly, Rabbi Yishmael's disciples themselves boiled the bodies of prostitutes to determine the exact number of bones in the human body. There are passages that describe the handling of various human tissues. There is a description of the sage who kept the skull of King Jehoiakam, of another sage who used the bones of his tenth son to comfort mourners, and of a third who wrote that he would "bury the dead and observe their bones," ostensibly to study the efffects of alcoholism. The statement about pig anatomy certainly implies a knowledge of human anatomy. In addition, a number of anatomic and pathologic observations support the likelihood that ancient physicians performed autopsies.

TABLE 1

Talmudic References Supporting the Validity of Autopsies

Nid. 30b	Rabbi Yishmael comments on autopsies on Cleopatra's slaves.
Bek. 45a	Disciples of Rabbi Yishmael study bones of prostitutes.
Mishnah	Detailed list of human bones.
Ber. 4a	Describes hands soiled through examination of blood, fetal tissue, and placentas.
San. 82a	Skull of King Jehoiakam saved.
Baba Bat 116a	Bones of the tenth son comfort mourners.
Nid. 24b	"Bury the dead and . . . observe their bones."
Ta'anit 21b	Pig anatomy is similar to human anatomy.
Nid. 55b	Position of the salivary glands.
Tomid 50a	Correct number of lobes of human lungs.
Nid. 24b	Correct number of bones in human body.
Nid. 24b	Color of bones.
Nid. 24b	Effects of alcohol on fat deposition.
Hul. 43a	Structure of the esophagus.
Git. 69a	Pulmonary hemorrhage compared to other forms of hemorrhage.

To turn to more modern times, we really do not know if Maimonides performed human autopsies himself. However, his comment that "those not acquainted with Anatomy think that nerves and arteries are the same, and, were it not for the study of Anatomy in which we are busily engaged, we also would not know the difference" shows that he understood very much the usefulness of dissection (Table 2).

Other Jewish physicians certainly did perform autopsies. Amatus Lucitanas was a sixteenth-century Jewish physician who performed approximately a dozen dissections and confirmed the existence of the azygos vein. Abraham Zacatus performed many dissections in the 1620s and described, among other things, plague, cancer, and bladder and kidney stones. Rabbi Jacob Zahalom was also a practicing physician. He did not perform autopsies himself, but it is written that he approved the performance of an autopsy to be carried out by a non-Jew on a Jewish victim of the plague in 1656.

By the seventeenth century, autopsies and anatomic dissections were being performed more and more often and cemeteries were plundered for a supply of bodies. Because Judaism requires the prompt burial of the dead, Jewish cemeteries were the best source for fresh bodies. What influence this played on future talmudic interpretations is not clear. It is clear, however, that a medicoreligious work by Tobias Cohn published in

TABLE 2

Selected Rabbinic Comments on Autopsy

Year	Name	Statement
1190	Moses Ben Maimon (Maimonides)	Distinguished between nerves and arteries.
1656	Rabbi Jacob Zahalom	Approved autopsy by non-Jew on Jewish plague victim.
1737	Rabbi Jacob Israel Emdem	Forbade dissection on sabbath and forbade deriving any benefits from human body.
1793	Rabbi Ezekiel Ben Judah Landau	Allowed autopsy only if someone "immediately at hand" will benefit.
1836	Rabbi Moses Schreiber	Said remote possibility of saving life should not override certainty of desecration of the dead.
1852	Rabbi Jacob Ettlinger	Found no justification in disturbing dead even if lives of other existing patients might be preserved.
1872	Rabbi Moses Schick	Warranted autopsies if lives of other existing patients might be preserved.
1905	Rabbi Dr. Hermann Adler	Lauded individual for having directed autopsy on himself at the expense of his estate.
1935	Rabbi Ben Zion Ouziel	Saw no objection to autopsy if carried out with respect.
1949	Rabbi Dr. Isaac Herzog	Israeli law of anatomy and pathology.

1707 illustrates a Jewish man with his viscera exposed and compares the body to the structure of a house, further supporting the view that autopsies were performed on Jews (see Frontispiece).

In 1737, Rabbi Jacob Emden was asked to decide if a Jewish medical student at the University of Goettingen could dissect on the sabbath. Rabbi Emden not only ruled that the Jewish student could not engage in his medical studies on the sabbath, but he added that it was forbidden to derive any benefits from human bodies. This decision, in the early eighteenth century, may well be the first formal interpretation to clearly suggest the inviolability of a human body and consequently the impossibility, in terms of the Jewish law as interpreted by Rabbi Emden, of performing an autopsy.

Rabbi Ezekiel Landau of Prague was a remarkable man of the latter part of the eighteenth century, fully devoted to the preservation of Judaic traditions but able to engage in productive dialogue with the non-Jewish society around him and to effect meaningful social improvements for the Jews of his community. Rabbi Landau had an inquiry from London: a Jewish man had died after surgery from a bladder stone. Was it permissible to perform an autopsy to determine the cause of death? Rabbi Landau's response was to the effect that autopsies could be performed only if someone with the same disorder was immediately at hand and only if some benefit to that person would clearly follow the autopsy. Morgagni's correlation of clinical observation and autopsy findings had been published only thirty years before and was certainly not well known.

Rabbi Schick, who was adamant in his resistance to reformist activities in the religious sphere, restated the Landau concept that allowed the autopsy to be performed if it could directly benefit an existing patient. Adler, chief rabbi of England at the beginning of the twentieth century, supported the use of the autopsy, as did the Sephardic chief rabbi.

After World War II, as the medical community in Israel flourished, cadavers were clearly needed for dissection and autopsies to augment clinical knowledge. An agreement was reached between the chief rabbi and Haddasah Medical School, culminating in a law of anatomy and pathology that was passed in the Knesset. Autopsies were permitted when the civil law demanded it, to establish the cause of death when it was doubtful, in cases of hereditary disease, and to save lives. This provided even greater latitude in the performance of the autopsy. In the last two decades, Rabbi Imanuel Jacobovits has written extensively about the autopsy. Formerly rabbi of the Fifth Avenue Synogogue in New York and now chief rabbi of the British Commonwealth, he has emphasized the extraordinary growth and scope of modern communications, which effectively allow a patient anywhere in the world to be considered "immediately at hand" and able to benefit from the autopsy. This view has not been uniformly accepted.

The autopsy is a vital and indispensable component of the medical care of the patient who has died. Without the autopsy, there can be no certainty about diagnoses, no effective evaluation of the therapy, and no guarantee of the quality of practice. The Judiac prohibitions against autopsy could not take into consideration the extraordinary benefits to humanity that would follow the effective use of the autopsy. Further, those prohibitions are not founded in the ancient laws, but instead reflect interpretations rendered in the eighteenth century by learned men who would surely recognize immediately and completely that the modern autopsy is not a desecration of the human spirit but is, instead, a testimony to the human desire to improve for the sake of all.

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Rabbinic Comment: Autopsy

Rabbi David M. Feldman

The announcement of this discussion of autopsy evoked several different reactions. One was, "I thought it had all been said already. What more is there to say?" Another, not so weary of the subject, was, "How can there be any controversy about autopsy in Jewish law when Judaism is so pro-medicine? If we Jews are so concerned with the saving of life, with saving a person from a possible threat to life, how can we view autopsy as anything but a *mitzvah,* a good deed, or at least a means to a *mitzvah?*" An allied response pointed to the Jewish obsession with research and to the idea that Jewish doctors love to do research, love to study medicine: "How can there be a Jewish religious prohibition or inhibition against the very idea of autopsies?" To some people, the issue itself was a question—should it be an issue at all?

But in fact passionate and tense debate has raged for some time. Dr. Geller has given us a fine overview of the Jewish involvement with dissection and postmortem autopsies. He has also told us of the practical problems and the accommodation, the concordat reached between Chief Rabbi Herzog and Hadassah Hospital as well as some of the other tensions between physicians and religious authorities in Israel and here in America. The tension is very real. The debate continues unabated and much remains to be said.

Broadening the background, the backdrop against which Jewish religion and the physician are involved in autopsy, the issue is not simply a clash between the medical inclination or tendency in favor of autopsies versus the Jewish inhibition against them. It is not that postmortems are forbidden because of a specific biblical or talmudic imperative which says, "Thou shalt not autopsy." Rather than a narrowly based prohibition, the Jewish view has a wider base of values, halakhic and some extrahalakhic.

Reverence for the Body. One of these values is reflected in the Jewish concept of reverence for the body, of not desecrating the dead. The concept has its beginnings in a biblical injunction that even the body of an executed criminal should not be left hanging overnight: "It is an abomination." Even the body of a convicted criminal, and certainly the body of a blameless human being, should be removed from where it was hanged, or where it died, and should be given burial, for the human body, even after its soul has departed, is to be respected.

The importance of proper burial can be seen in Jewish law on bereavement practices. As a synagogue rabbi, I am much involved with mourning laws and customs. A kind of secret that I don't tell the members of my congregation—it would come as a surprise and even as a disappointment to them—is that according to halakhic rulings, the mourning period is not as stringent a requirement as is speed of burial. If someone were to say, "After my death, don't mourn for me or recite the *Kaddish,* the prayer for the dead, for me," grounds can be found for allowing the request. From the standpoint of the Talmud, certain practices are regarded as "for the sake of the deceased" and others as "for the sake of the bereaved." Elements of both are involved in mourning customs. We mourn for the honor of the person who has died, but we also mourn for our own sake, to give ourselves a chance to work out our grief, to accept comfort and consolation. Proper burial is an entirely different matter. Someone might say before he died, "Don't bother burying me. Don't bother having funeral services. I want to be cremated." The law is, ignore his wishes because the Bible says "you must bury him," which is interpreted in the Talmud to mean

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that it is not up to him to say, "Don't bury me." This is a *mitzvah*, a religious duty, which is objective, which has to do with our own respect for the image of God in the body, our duty of reverence for the body. No one can choose to waive that particular privilege. No one can ask you to cremate him; you are under obligation to give him proper burial, proper respect for the body, in objective not subjective terms. That is one aspect of the halakhic and extrahalakhic bases for values.

Another such aspect is a very touching concern with burial of a stranger. The phrase *met mitzvah* is a technical term for one who has died without known relatives. It is a religious duty for the entire Jewish community to act as the relatives of someone who dies that way and see to his proper burial. This, in turn, is based on a concept that the proper treatment, the proper disposition of the body after death is not just kindness, but the only true kindness. It is a most altruistic thing, this service to the dead. Any other kindness is colored by the consideration it may entail some expectation that the kindness will be repaid. Any act done for a living person can never really be altruistic as long as that person may repay the kindness. But with a deceased person, the kindness is sincere; it is a true kindness, one from which you expect no reward, no reciprocation.

Attending to the burial of an unclaimed body or a body with no known relatives is, moreover, not only a kindness, but is so important that even the high priest is supposed to violate the ban on defiling himself by contact with the dead. A Kohen, one from the priestly family, and certainly the high priest, is forbidden to have contact with the dead. He is forbidden even to go to the cemetery, except for immediate relatives. But if the high priest chances upon an unclaimed body, even he must violate that ban on self-defilement and occupy himself with giving proper burial to this body.

This emphasizes the fundamental importance in Judaism of proper burial, which bears on the question of autopsy. Judaism protects the fetus because it cannot fend for itself; Judaism also is concerned with proper burial, another aspect of looking after those who cannot fend for themselves. The medical profession is concerned with autopsy for the advancement of medicine and even for the saving of life, while the Jewish religious community is concerned with these aims but also with the concept of reverence for the body, of protecting this vulnerable body that cannot fend for itself. Hence, it is understandable why the two communities are at odds on autopsy.

As if that were not enough, a kind of overlapping exists. Dr. Geller speaks of the Jewish religious mandate for autopsy, and rabbis speak of the medical necessity and value of performing autopsies when indicated. The medical and the Jewish religious community are both concerned with those areas in which there is a common objective. In my experience those persons who oppose autopsies for themselves or for their relatives are not necessarily the most observant Jews. They may violate every other religious requirement, but when it comes to an autopsy for a near relative, they'll balk and stand up for religious principles. They'll say, That does violate my sensitivities and my reverence for the body. At the same time, doctors are moved by the possibility of helping others through the knowledge they can gain from autopsy.

Two religious physicians in Jerusalem took opposite yet complementary views on autopsy. One concluded that the whole issue has now subsided; we Jews have now resolved the arguments against autopsy. The other, Ya'akov Levi, an outstanding endocrinologist, wrote that we have already derived sufficient benefit from the anatomy dissections we've already performed; the star of anatomy is sinking. For results that help patients, think of penicillin, think of heart operations, think of the polio vaccination—the knowledge necessary for these advances came not from autopsies at all, he writes, but from biological, chemical, and x-ray research. So don't be so sure of your claim for religious and humanitarian benefits from autopsies, Ya'akov Levi concludes.

The Landau Ruling. The celebrated case that Dr. Geller referred to, the landmark responsum of Rabbi Ezekiel Landau, has had an interesting history in both camps, the medical fraternity and rabbinic interpretation. As Dr. Geller says, Rabbi Landau was asked whether autopsy was permissible on a particular patient. The rabbi said no in the particular case, but yes, autopsy is permitted, where, as he put it, there is another patient who needs that information, literally, another patient "at hand," or "before us." That would constitute life-saving reason for violation or setting aside of the principle of reverence for the dead.

"The saving of life sets aside the entire Torah." Not only may one eat on Yom Kippur, the Day of Atonement, a fast day, if life or even health is threatened, but one is mandated, commanded to do so; it becomes one's moral duty to eat rather than fast to keep body and soul together. Here, too, if someone is "before us," at hand, the mandate is to violate other provisions of the Torah, such as reverence for the body, and do what is necessary to save a life.

Subsequent rabbinic authorities have carried this ruling further and have said that, in light of modern technology, everybody is "at hand" throughout the world. Because the results of an autopsy in a hospital in London can be telegraphed or electronically transmitted to a hospital in New York, Jerusalem, or Vienna, so the whole world is now "before us." We are all, in Marshall McLuhan's phrase, part of a "global village." The extension of the ruling is attributed first to Rabbi Hayyim Ozer Grodzinski, who died in 1940. He flourished in this, the modern age. Images remain in my mind of what I've read about him, answering questions on the telephone, two telephones at a time—with a telephone in each hand he answered questions put to him from all over the country, or from wherever else callers could phone from. So it makes sense that this great rabbi, who himself had experienced the benefits of technologic improvement, was the one who would say that technology has "interconnected" the whole world.

Resurrection of the Body. Some Jewish believers will not take advantage of the law's leniency or requirement. They have inhibitions or superstitions or genuine questions about allowing autopsy for their next of kin that even a religious ruling does not help. In matters of birth control, too, I have found that certain couples will not avail themselves of the halakhic permission to practice contraception. They hesitate to consciously, deliberately, directly interfere with that natural process of birth, procreation, pregnancy. Children are a gift of God, and how can you interfere with something so providential as that? It's best to desist from any kind of preventive action and leave it in the hands of Providence. Those who feel the same way about autopsy persist despite the most learned and persuasive permission from the halakhists, who are, otherwise, conservative or strict.

Sometimes the question of the resurrection of the body, which is a teaching in Jewish philosophy, as opposed to the immortality of the soul, plays a role in resistance to autopsy, as a kind of subliminal factor in thinking. The resurrection of the body figures in Catholic law as well. A question was directed to a former pope: in the circumstances of a shortage of burial space, could one then cremate the body? The answer was that cremation is ordinarily a defiant act, a way of saying, I don't believe in the resurrection of the body.

Maimonides was not too comfortable with the Jewish teaching on resurrection of the body. Leaning more to the spiritualist side, he preferred the notion of immortality of the soul. He said that resurrection of the body is a doctrine, and therefore it's going to happen, but it won't last long—there will be a resurrection of bodies, then they will return to their former state; in the end there will be spiritual immortality. Morris Rafael Cohen, the famous professor of philosophy at City College of New York, used to say, perhaps facetiously, that he didn't understand why Maimonides was unhappy with the concept of resurrection of the body: "Immortality of the soul is something that I've never seen; I've never seen a disembodied soul. But I have seen a body and a soul together, so it's easier for me to visualize the resurrection of both body and soul."

The pope's answer to the question of whether cremation is allowable was that if the motive is to deal with a shortage of burial space, fine; but if the motive is to show defiance of the notion of resurrection, then cremation is not allowable. Similarly, Jewish philosophers in the Middle Ages, Saadia Gaon and others, were frequently taunted by questioners who would pose the problem of a person devoured by a beast, who was in turn devoured by another beast, the latter in turn destroyed in a fire, and so on—what happens to the body at resurrection? The answer was that, since it's a miracle, it can happen from any state of decomposition and from any state of disintegration. Yet some persons retain a subliminal apprehension about preserving the body, and hence resist the idea of autopsy. We want to respect these sensitivities, but we certainly don't want to respect them at the expense of legitimate, logical, affirmative Jewish values that give us an overriding mandate to save life in the face of other, lesser considerations.

Other Allowable Postmortem Procedures. Other qualifications to the ban on autopsies have been made. Rabbi Moshe Feinstein, in an effort to make autopsies possible in more cases and yet maintain proper Judaic conditions, has ruled that inhibition against desecration of the body is not violated by such practices as needle biopsies. Just as the physician uses a needle during lifetime for amniocentesis or other biopsies, a needle biopsy after death performed without opening the chest or the abdomen would not constitute a desecration of the dead. Nor does taking blood samples after death by a needle puncture constitute a violation. Also, peritoneoscopy, by which organs are studied through body cavities, again without dissection, is also permissible as a way to gain information otherwise obtainable through autopsy of a more gross kind.

Also acceptable from this standpoint is taking photographs of the gross organs for further study as an alternative to preserving the organs to be studied beyond the time of burial. A way of realizing the goals both of medicine and Jewish legal teaching, preserving mutual respect and cooperation, is opened here.

Medical-Religious Cooperation

In medicine as in other walks of life, there is a difference between a statesman and a politician. The statesman makes broad philosophic points and the politician tries to implement them. The medical ethicist tries to uphold certain principles despite the ad hoc desire or need, even the tunnel vision, of the medical practitioner. The latter is interested in a specific case and is convinced that an autopsy is very much desired and necessary, but the ethicist reminds the physician of the broader view, that haste in recourse to autopsy violates other principles which are precious to us, such as reverence for the body in the abstract.

Cooperation by both advocacies will also ensure that only minimum operations, performed on the dead body as quickly as possible, will be undertaken and that the autopsied organs will be brought to proper burial afterward—under conditions of solemnity rather than levity (as Rabbi Jakobovits reminds us).

Hence, without blanket surrender of bodies to the hands of the anatomist for dissection, we can have both the advancement of science and the ideal of saving life, preserving the religious values of protecting the unprotected, protecting the dead who cannot fend for themselves. The concept of reverence for life gives us humanity. We lose our humanity unless we do have these concepts of reverence and sanctity.

Although Ya'akov Levi has identified biological, chemical, and x-ray research as the major source of modern knowledge, there remain the great scourges, cancer and heart disease. The battle against them can be better pursued with greater knowledge of all kinds. There is now far more interconnection between the medical disciplines, and the knowledge of one particular disease can help banish other scourges. So it is wise to broaden the concept allowing autopsy enunciated by Rabbi Landau. At the same time, we need to safeguard against indiscriminate autopsies, against autopsy without due concern for the sentiments and feelings of the people involved, against the right to autopsy without the qualifications I have noted. Attending to both halves of the medical-religious equation, with mutual trust between the two opposing interest groups, will advance the proper goals with benefit for all.

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Old Age: Right to Privacy and Patient's Right to Know

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There is a great landscape between adolescence and old age. I do not cover here adult development in the early and middle phases, however, concerning myself primarily with old age. What I say about the later years does have applications to those earlier phases of adult life, including any occasions in which dying or death occur.

Under discussion are the right to privacy, the right to know, and the right to be involved in decision-making. Many physicians share the negative attitudes of our culture toward older persons. The contemporary life conditions of many older persons, vulnerable, ill, or disabled, are frightful. Perhaps, especially in America, attitudes and socioeconomic status profoundly influence the care of older persons. They are frequently denied the rights under discussion.

With the exception of faculty members at medical schools, physicians are not famous for being great communicators. Rather, they enjoy being mysterious and are not too interested in being informative when talking to their patients. This is especially an issue for older persons who grew up during the medical era in which the physician was an ultimate authority. The apostolic function of the doctor was very powerful. Therefore, many older persons find it difficult to bring up certain topics or to question the physician. An older woman might be embarrassed, for example, to discuss incontinence of urine. When physicians do communicate with older patients, there may be so much anxiety that it is difficult for the older person to fully comprehend what is being said.

Older persons are stereotyped. "What do you expect at your age? You get older, you have to suffer," says the physician. I am reminded of Morris Rocklin, a 92-year-old volunteer who I began to follow in 1955. I last saw him when he was 101. He died when he was 102. At age 101, he told me about seeing his physician to complain that his right knee hurt. His physician said, "For heaven's sake, what do you expect at your age?" At which point Morris said, "Now look here, my left knee is also 101, and it doesn't hurt."

We physicians must be as comprehensive in our evaluation of an older patient as we are of patients of all ages. We cannot write off an older person as a "crock." I first heard the word "crock" at medical school; many similar terms are in wide use—"gomer," "gork," "dirtball." Those who claim these terms are not used anymore should read Sam Shen's book, *The House of God*. These tasteless epithets express powerful attitudes that really reflect our own helplessness as physicians. These attitudes interrupt our capacity to communicate effectively with older patients. They do not assist older persons to know what they need to know and to make the decisions they need to make.

One central point involving doctor and patient is the advisability of active treatment. Paul Beeson, the distinguished American physician, has expressed his deep concern about the application of "no-code" and "do not resuscitate" orders to older patients in American hospitals. The issue of "pulling the plug" or "turning off the machine" is important. But it needs to be considered explicitly, not covertly. We know very little about the terminal period and the circumstances of dying. I can find only one significant book, Cart-

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wright's *Life before Death,* that deals with the last days of life.

At the National Institute on Aging, we tried to develop a major study of the last days of life: How and under what circumstances do people die? Do they have pain? What kind of medications have they been given? Do those medications include analgesics? Were they expected to die? Did they expect to die? Was the death sudden? Was the person aware of death or was he asleep or in coma?

We exploit the politics of anguish to raise funds for research. The efforts of the "cancer lobby" to scare us have succeeded. Most people believe that if you have cancer you will have pain. Most data, however, suggest that perhaps no more than one-third of cancer patients have significant pain. On the other hand, individuals who suffer from heart disease (and half of the deaths in the United States are due to cardiovascular disease) suffer from anxiety, breathlessness, and pain, yet those distressing symptoms have not been dramatically presented by the "heart lobby."

We need to know more about the last days of life as we evaluate the three issues under discussion. Do we know whether there are disproportionate expenditures of funds associated with terminal illness? There are no sophisticated, comprehensive studies to answer this question, although many people believe too much money is being spent in heroic, unnecessary efforts. There are such occasions, but the extent has not been documented. Unfortunately, we even have difficulty defining exactly what a terminal illness is. Many a patient has surprised us by not being terminal at all.

Discussion of the importance of the last illness intensified during the Carter administration when a white paper came to light in the pages of the *Washington Post.* The white paper suggested that, since 20% of all Medicare costs are associated with the last year of life, we could save money by encouraging older persons to carry death with dignity (right to die) cards with them and speed up their ultimate dying process, all to the public good.

The last illness has probably always been the most expensive illness. There has been a failure to appreciate postponement or deferral of the costs that used to be associated with the diseases of earlier life. We have seen spectacular reductions in maternal, childhood, and infant mortality rates. Eighty percent of all deaths now occur after sixty years of age. Eight out of every ten newborn children are expected to live beyond their sixties and complete what we think of as the normal life cycle. One hundred fifty years ago, only one out of every three infants could expect to survive past 60.

Ethically, in medicine we should ask ourselves if everyone should receive equal treatment or if special treatment is warranted in some cases. My partner Rabbi Gordon discusses the Fourth Commandment. Should the aged and dying receive special attention? Life in itself is a primary value. We have to understand the special values associated with late life; the capacity to be a sponsor, to leave a legacy, to be concerned about young people. There are certain psychological needs—to put one's house in order, to effect reconciliation. If the physician or nurse assumes and covertly operates as if life per se or certain needs are not as important to older persons, older persons may be denied opportunities to complete certain major objectives of their lives: completing a reconciliation, attending the graduation or the birth of a grandchild. These are important human matters.

We desire some control over our own dying, but it seems to me we have become inordinately preoccupied with the "good death," rapidly translated into the "easy death." The dying are supposed to be spared pain, to be sheltered from any kind of turbulence. We shortchange ourselves. We need to have a sense of the reality of our own dying and death. I don't mean to be insensitive to the realities of pain and despair, but we can go too far and cosmetize the process of dying. Analgesics may impair our ability to speak to a loved one, to communicate important feelings. They may reduce participation in decision-making.

We can also reduce decision-making by patronization and infantilization of the older person. We may pat them on the back and reassure them if they feel guilty about something they did in their life. However, the person is dealing with *real* guilt. There are dramatic reasons to come to terms with acts of omission or commission that can reasonably be expected to cause guilt. We do no service to older persons by facile reassurance.

Should the older person's privacy be breached by extending information to the family? In my judgment, the answer in most cases is no. Older persons are not children. Physicians must obtain permission to share the older person's life and medical findings with the family. I frown upon the common practice of communicating with the children rather than the older person. The interests of the parent and the child may even be in conflict. "Don't operate on my mother" may not be consonant with the desire of the older person.

Many older persons do not have a physician. There are studies that suggest that no more than 10% do. People tend to have a physician older than themselves and, therefore, lose their physician through retirement or death. Also, people may delay seeking another physician until a crisis occurs. Thus, the opportunity for developing a relationship with a doctor may not exist.

One special issue is the question of informed consent as it bears upon research on senile dementia. As Lewis Thomas has said, senile dementia is the "disease of the century." It is a profound, devastating disease that afflicts 4%–6% of all people over 65 years of age. Of the 26 million people over the age of 65, one and a half million are in nursing homes with senile dementia, constituting 50% of institutionalized older persons. We must learn more about this disease. There are some exciting findings about neurotransmission. But can physicians ethically study and manipulate central nervous system physiology in patients who may be unable to give informed consent? Is it a disease that by its nature prevents us from properly studying it? We became concerned about this issue at the National Institute on Aging and therefore we developed a task force that included ethicists, philosophers, physicians, researchers, and lawyers. We developed guidelines, not regulations, which, among other things, urged that incipient cases of senile dementia not be institutionalized. To minimize coercion, the physician caring for such a patient ought not also be the individual conducting research.

A second special issue is the nursing home situation. In the care of frail older persons in the United States, the nursing home is dominant. There are one million people over 65 in 19,000 nursing homes. On any given day, more patients are in nursing homes than in hospitals. But the nursing home has not been in the forefront of the thinking of American medicine. In fact, only 17% of doctors visit nursing homes; or, to put it another way, 83% of doctors do not enter nursing homes.

There is a good deal of denial and a lack of adequate preparation of the patient for admission to nursing homes. The first death is a psychological death. Family visits steadily decline, out of guilt, conflict, feelings of hopelessness and futility. The second and final death comes some time later—some 22% of people in nursing homes die well after they have lived in the home three years. Thus, a mistake in diagnosis is indeed unfortunate—as is the patient's nonparticipation in the decision.

We hear a great deal about austerity. We are practicing politics of austerity, in which older people are made to feel uncomfortable if they should cost society money. We are practicing triage, which was originally developed for use during battlefield, not peacetime, conditions. A conference at Duke University recently reported upon in the *New England Journal of Medicine* suggested that we now have a multitiered health-care system. One participant said, "Well, that's all right. In air travel, there's first class and there's coach." No one pointed out that air travelers use the same airplane with the same pilot.

Why do we collaborate with the politics of austerity? Such thinking could quickly move us to immoral decisions. For example, some 8.8% of Medicare beneficiaries account for 70% of all Medicare expenses. Nearly 40% of eligible beneficiaries do not claim any Medicare expenses at all. We could soon acquiesce in a kind of "final solution": a simplified exit from this earth would spare society the expensive burden imposed by old age.

Older persons today are pioneers. There are an increasing number of them and they are developing different styles of existence and social roles. In the year 1900, the average life expectancy was 47. Today, it is 73. In 1900, only 3% of the population was over 65; today it is nearly 12%—and the numbers and proportion will get even larger. We have much to learn from older persons, and they have a responsibility to help shape the kind of future those who follow them will have.

We should be truthful to them, recognize their rights to privilege and confidentiality, and involve them in the decisions that affect them, even during the last months of life.

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Rabbinic Comment: Old Age: Right to Privacy and Patient's Right to Know

RABBI MACY A. GORDON

I was at first somewhat puzzled by the intellectual division between adult and aged. Infants have no privacy and cannot offer consent—unlike adults. Adolescents are distinct from adults and certainly from infants. But an aged person is, after all, an adult. If competent, an aged person must be included in any discussion of adults. If the aged person is incompetent or comatose, one might make a legal and moral comparison with infancy, again precluding the need for a separate category.

What I fear is that the distinction between the adult and the aged is not based on either medical or legal criteria, but on social attitudes toward the aged—attitudes which have changed considerably over the years. Here, the problem becomes very distinctly an ethical rather than a medicolegal one. In the preface to his excellent but very disturbing book *Why Survive? Being Old in America,* Dr. Robert Butler notes that "in America, childhood is romanticized, youth is idolized, middle age does the work, wields the power and pays the bills; and old age, its days empty of purpose, gets little or nothing for what it has already done. The old are in the way, an ironic example of public health progress and medical technology creating a huge group of people for whom survival is possible but satisfaction in living, elusive."

From that perspective, the aged do indeed have problems that are different from young adults, who have years of future life to consider, who interact with a growing family often dependent on them, and whose utilitarian value to society is unquestioned. I am as uncomfortable as Dr. Butler is with that distinction, real though it may be. In a conference, a separate section on the aged suggests that we think of the aged as something other than simply adult.

While the attitudes of adults and attitudes towards adults may vary based on the stage of adulthood, it is eminently clear from both a legal and ethical point of view that the right of the patient to be involved in decision-making is vouchsafed.

Informed Consent. I deal first with the problem of informed consent as it relates to adults.

The obligation of a physician to obtain informed consent from the patient is a relatively recent one. A valid consent has become a legal necessity in contemporary medicine. Valid consent is generally acknowledged to consist of three elements: information, freedom, and competency. In other words, a consent is valid if it is obtained from a patient who is mentally competent, free from constraint or coercion, and knowledgeable about the proposed therapeutic program. Informed consent is, of course, based on the right to know. The underlying principle of requiring consent is that of patient self-determination.

Much of the recent literature in medical journals about informed consent discusses it from a legal rather than an ethical perspective. The question is not "Is this the right or wrong thing to do?" but "Am I legally protected if I do, or don't make a full disclosure and obtain proper consent in this situation?" The numerous malpractice litigation based on the lack of informed consent, the court decisions in recent years, and the increasingly general social trend favoring self-determination suggest that the ultimate practice of medicine in any of its forms rests with the person who is the object of medical intervention.

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Older traditions of medical ethics generally do not share this premise. Rather, the question of informing the patient was viewed from a variety of other perspectives. In the Jewish tradition, informed consent is not always essential. The principle that the physician acts with divine license to heal actually precludes a requirement of consent, for just as it is the obligation of the physician to heal, so is it the religious and moral obligation of one who is ill to seek healing. The patient who refuses a reasonable and appropriate medical regimen, whether through wilfullness, despondency, invincible ignorance, or irrational fear, is in violation of a divine trust. Physicians acting in what they know to be the vital interests of the patient's physical and mental health are not subject to either religious or ethical sanctions if they do not obtain consent, regardless of the patient's own attitude.

In formulating what I see as the Jewish ethical stance, I am not advising physicians to undertake therapy without obtaining consent, or to violate the law of the land as adjudicated through the courts. The physician is well advised, both from a moral and a practical point of view, to obtain informed consent whenever possible, but not to jeopardize the life or health of a patient by undue delay.

However, informed consent does represent a moral issue in Jewish thinking, though not in the same sense as understood in Western law. The morality of requiring informed consent finds expression in Jewish tradition in the recognition of a very human phenomenon—physicians, like all people, sometimes have personal biases. Therapeutic decisions are sometimes based on intuition rather than fact. Physicians may feel so strongly about the need for a specific procedure that they are unwilling or unable to perceive accurately the merits of alternative procedures. The patient who is reasonably sophisticated in medical knowledge, or who has competent advice, may disagree with the approach taken by a particular physician. The patient has the right to hear the views of the physician cogently presented, to weigh the alternatives, and to make a personal decision between alternative courses of therapeutic action. It is not the right to be wrong that the patient enjoys, but rather the right to choose the course of therapy in which he or she has the greatest confidence.

Clearly the doctor-patient relationship is asymmetrical in power and risk. Patients seek doctors when they are sick and vulnerable. The asymmetry is especially compounded in the case of the aged. Patients entrust to physicians not only access to their bodies, but also carefully guarded secrets and fears. Educating patients about the nature of their illnesses and the therapeutic regimens suggested is an effort to lessen the asymmetry and emphasize the mutuality of the relationship. Patients should recognize within their physicians not only the expertise that is the result of professional training and experience but also, it is to be hoped, the humility of one who recognizes the strictures and limitations of human fallibility.

The same moral obligation that permits the patient to choose also permits—indeed mandates—the physician to try to convince a patient of the best course of action. When the doctor's certainty is challenged by the patient's stubborn refusal to see the obvious, to accept the facts or face realities, the doctor has the moral right to call in others: the family, the clergy, certainly the rabbi in the case of a Jewish patient, and to seek assistance in the ethical dilemma. The rabbi who acts under the norms of religious commitment to a coreligionist, rather than under the usual legal strictures that govern the medical profession, is less suspect of having a detached self-interest. Although paternalism by a physician may be morally suspect except in rare cases, paternal counsel is often accepted from a rabbi or the clergy. Therefore, when a physician has difficulty obtaining a needed consent, the ethical suasion of the rabbi should be enlisted. This is not conning a patient; from a Jewish point of view, it is an effort to teach people "what is right, and what the Lord God doth require of thee."

The Right to Know. Properly informing an adult is prerequisite to obtaining consent. A somewhat different ethical problem is created in the situation in which no consent is needed or required, but the patient wants to be informed of a specific diagnosis. What is the obligation of the physician and what are the rights of the patient to be told of diagnoses that are pessimistic in the extreme?

Learning of imminent death is certainly one of the most traumatic moments of life. To impart such information to a patient or to the family is a responsibility that should be approached with trepidation. To the extent that this information may cause great nervous stress or emotional harm, lead to despair, or endanger what is sometimes called the "will to live," the information is simply not a "right" of the patient. No person has the moral right to endanger themselves, even if that risk is mental or emotional rather than physical. The subject is to be approached, therefore, according to Jewish ethics and law, not from the legal consideration of the right to know but from the perspective that weighs the wisdom, necessity, and purpose of imparting such information. This decision is not the exclusive right of any one individual but should probably be determined by the physician in consultation with the clergy and members of the family.

The problem of informing a patient is not a new one, nor has the technological sophistication of modern life-prolonging techniques made it a less emotion-laden task. Jewish tradition, from the most ancient times, has expounded two principles in this regard. First, a patient should never be informed of anything that may impair or contribute to the deterioration of the patient's physical or mental well-being. Second, to quote a talmudic passage, "When he takes the turn towards death, one should say to him: 'Confess. For many have died without confessing. And many who confessed, did not die. And perhaps in the merit of confession, you will live.' " In essence, the Jewish view is to maintain the proper balance between these two religious dicta.

On the one hand, the well-being of the patient requires that people not upset or burden him or her with the distress and apprehension of being informed. Even members of the family who may unwittingly permit their tongues to slip should be kept uninformed. On the other hand, the sophisticated patient is often aware of the seriousness of the situation without formal pronouncement. One cannot nowadays spend days in an intensive-care unit and receive radiotherapy or chemotherapy and remain blissfully unaware that one's life is at stake. In such a condition, the patient who is emotionally able to appreciate the situation should be given every chance to set their house in order both financially and spiritually. The counsel of physician, rabbi, social worker, and others should be couched in appropriate euphemisms to avoid jarring patients or disturbing their sensibility. Strong and well-adjusted patients may even find it necessary to console and strengthen members of their own family.

Many physicians favor not telling patients that they are dying. Different studies have yielded different results on whether the patient in fact wants to be told. It appears to me, in any event, that no general rule in this matter should be based on statistical findings. The welfare of the patient should be the paramount consideration in determining just how much should be told, when, and by whom.

Such modern concepts as the "right to die" and "death with dignity" are a separate study unto themselves in the field of medical ethics, decisions that follow on the right to know and the right to privacy. But in discussing the right to know, it is perhaps important to express a very basic Jewish idea that has echoes not only in law but in anecdote and folktale.

It is not the province of medical science to set limits to life. While it may be statistically possible to predict life expectancy at various stages of a disease, no purpose is served by guessing at what is tantamount to a death sentence. The physician has divine license to heal, to the best of his or her ability. To act beyond that calling is to usurp power not given; in effect, to play God. While there are circumstances in which general time expectations of the normal course of the disease might be shared with mature members of the patient's family, the element of hope should never be put aside, lest the morale of the patient be weakened, or the will to live be undermined. Many patients know without being told and seek a share in setting a regimen for terminal care.

Telling the patient is an art. Time should be given for patients to come to their own conclusions and let facts sink in. Patients must have an opportunity to talk about their fears, doubts, and frustrations. They should not feel alone, and rabbi and physician should give all the physical and emotional support at their command, in keeping with their compassionate roles. Alternative possibilities, other scenarios, straws at which to grasp all assume the proportions of life-support systems to the terminally ill patient.

The decision to inform is, therefore, never based merely on the right to know. It is a carefully weighed decision that determines not only whether to inform, but when, where, why, how much, and by whom. Both physician and ethicist should always adhere to what has been called the first rule of medicine, and what may well be a cardinal rule in medical ethics: *Primum non nocere:* "the first rule is, do no harm."

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End of Life: Discussion

Moderator: Donald Gribetz, M.D. Discussants: Robert N. Butler, M.D., Rabbi David M. Feldman, Stephen A. Geller, M.D., Rabbi Macy A. Gordon, Ira Greifer, M.D., Rabbi Moshe D. Tendler, Ph.D., and Rabbi Isaac Trainin.

Questions were posed by members of the audience and were read by the moderator.

Geller: Rabbi Feldman and I spoke a number of times before this meeting to make sure we would not engage in a battle with swords drawn. We do not have, from either the medical or the Judaic point of view, a great conflict of ideas. Basically, the one concern that both of us embrace is that life must be preserved. Rabbi Feldman will agree that, in many cases, we may differ some in degree. But, in many cases, the autopsy is indeed a *mitzvah,* is indeed a benefit to human beings in general and to Jews.

Autopsy

Feldman: We seek that area in which the agreement takes hold. It takes hold in trying to preserve the individual's sanctity. Autopsying someone for the greater good of medical science would seem to be, subjectively, an extravagant use of one person for the general good. We meet on common ground when somebody's life is dependent upon autopsy right now. Then concern for the intactness of a body is not sufficiently strong to override the mandate to save life. On the other hand, if you carry it too far, a person just has no say over his body—it can be used for all kinds of cadaver dissection for study, which is going too far in the opposite direction. We want to find the meeting ground on which the person is used for a directly life-saving purpose and in which use of the person is under certain controlled conditions. Our Medical Ethics Committee several years ago formulated an autopsy request form on which doctors would stipulate the reasons for the autopsy. Autopsy conditions would be reverent, quick, and minimal. Most important, all organs must return to the body for proper burial, because the same requirement of burial extends to each organ. Whatever is taken out for autopsy must be returned. Our committee, understanding both the medical and religious imperative for autopsies, tries to control the conditions under which autopsy is done by formulating that paper.

Tendler: I would like to clarify a couple of points. One is that autopsy that satisfies the "here and now" principle, that is, offers a direct benefit, is well in keeping with Jewish Halakhah, the law. The big problem in every medical school in the world is that the teaching of autopsy presents great religious ethical problems to the Jewish tradition. As Dr. Geller explains, a child dies and you want to know if there is a genetic disease. Or a patient dies and you want to know if he had tuberculosis so you can treat the rest of the family. These are the easy cases. The difficult one is the "go fishing" autopsy which, as Dr. Geller correctly pointed out, has benefitted humanity so much. We have learned much from it. The question is, how can we, within the traditions of Judaism, justify the "teaching" autopsy? What conditions have to be set to permit any autopsy? The conditions for maintaining an aura of dignity and respect really have to be legislated by the hospital or by the chief pathologist. Beyond that, the basic issue is how much of the concept of human dignity, which we feel is violated by the autopsy, are you willing to give up to benefit society through the research value of the general autopsy? I would like the physician to be educated "here and now" at the same time that I am being educated.

Dr. Feldman's brief analysis of Maimonides' attitude toward resurrection of the dead needs further elaboration. The resurrection of the body, not of the soul, that Maimonides had difficulty with is considered one of the thirteen articles of the faith enumerated by Maimonides.

Question: What about the proposition concerning the general autopsy?

Tendler: There never was a justifiable recommendation for general autopsy. You have to handle it as a total problem. Consequently, we must decide what part of autopsy work is absolutely necessary, and what kind of autopsy work we are willing to give up. We give up the present benefit of general autopsy because of the greater good of maintaining the dignity of the human body.

Geller: One of the problems is that the lay public and the medical profession are laboring under a gross misapprehension that we live in modern times. What we are doing in medicine is still to some extent in the dark ages. Obviously, if we have to think about things like cutting people open to make them better, we're still working at a rather primitive level. I venture that most autopsies, certainly those done at this institution, are not fishing expeditions. Rather, they answer some important questions that potentially benefit all of us. Why did the patient die? Was the diagnosis right? Did the doctor, who is going to take care of living patients today, tomorrow, use his or her knowledge to the best advantage? Did he or she select the best therapy? Did the diagnostic tests that we pay hundreds and thousands of dollars for produce the correct information? Was the CAT scan accurate? These are the key questions that can only be answered by an autopsy that can only benefit human beings.

Anecdotes are not evidence, they're anecdotes. Here is one, about two patients at Mount Sinai Hospital within the last three years, both of whom had heart surgery. The first patient died with a completely nonunderstood infection of the chest wall, a terrible infection that literally ate away the chest wall and eventually involved the entire body. All attempts to diagnose this were to no avail. The patient had a very rare fungal disease which has been seen at Mount Sinai only about 40 times in the last 20 years. It is a very rare entity and it was only found at autopsy. Not immediately at hand, but three weeks later—which is pretty close—another patient came to the cardiac service for cardiac surgery. The patient had successful surgery, survived, and developed something that the doctors immediately recognized was very much like the fungus that had killed the man three weeks before. They treated him, he went home.

There is another part to this anecdote. This very rare infection was then traced, both at this hospital and other hospitals, to a certain type of gauze that is favored by cardiovascular surgeons, elastic and therefore not subjected to the usual sterilization methods. This center was one of the first to recognize that this type of gauze which cardiovascular surgeons favor is the carrier for this type of fungus. The disease has ceased to exist at this center.

Greifer: The one argument that seems to prevail is that autopsies should benefit patients now and in the immediate future. In this day and age, many of us know that certain chiefs of pathology do autopsies by what I call push-button techniques. Autopsies are done by people who are not involved with the Judaic-Christian codes in many ways—for example, with levity and lack of respect for the human body.

Tendler: We have no right to take a patient's body without his or her permission, just as we cannot take a person's possessions without permission. In Jewish law our respect for life, our need to save life, is so dominant that we are willing to do away with all human-to-God relationships, but not with human-to-human relationships. I cannot break into your home and steal your sabbath candlesticks because a friend of mine needs a heart transplant. That is never permitted under any condition. It is not true that saving a life is more important than all prohibitions. All prohibitions between humans and God? Yes! I can suspend sabbath laws, Yom Kippur laws, but I cannot violate your rights even if my rights seem to be involved with saving my life. One key principle is that you cannot, even for a good reason, take an individual's possessions. In Jewish law, a man loses all possessions when he dies except his possession of his own body. That he has a right to. If under present conditions a person offered a blanket permission for his or her body to be used in accord wtih Torah law, rabbis could decide that this is life-saving and is permitted. It still requires a person wanting to do a *mitzvah,* a good deed.

Question: To clarify several questions, if somebody were to die as the result of an accident, a sudden death, and the family is ready, willing, and able to donate that person's organs, would donation be completely forbidden in Jewish law?

Tendler: I know of no way in the protocol of Jewish law to permit such a thing unless a donor card is signed or family and friends certify that the deceased expressed this wish.

Question: What would be the prohibition in Jewish law?

Tendler: This prohibition is clearly analyzed in the Talmud.

Question: Would it be proper and helpful if some sort of a *mashgiach* (religious supervisor) were present at an autopsy? We do have *mashgiach* present at the slaugher of animals. Is there a rabbi employed by the office of the chief medical examiner in New York City to witness autopsies?

Tendler: The Jewish chaplain of the hospital is often involved. He is the only official. Certainly there is no chaplain in the medical examiner's office. Doctors don't have to be supervised; that would be insulting. They do have to undertake to follow the guidelines we formulated on the Medical Ethics Committee—that autopsy will be quick and minimal and will not delay burial, that all organs removed will be returned to the body for burial.

Greifer: Then to interpret Rabbi Tendler, if an individual deeds kidneys or cornea to another human being, the family would be incorrect, no matter how strongly they object, in preventing the donation. Such a requirement would also prevent an individual of such belief from accepting a kidney from someone who did not give permission in the first place. If a person passes away, the family gives permission, the kidney is available. If someone is of the belief that you stated, is it correct for them to receive the kidney?

Tendler: The second case is the problem of the fence in Jewish law. Someone steals something and a fence wants to sell it to me. I want to buy it from the fence. That is a complicated procedure. Obviously, it is less than stealing directly, but your interpretation of the first part is correct. It is not the family's business to donate or not donate someone else's kidney. The family cannot make the donation. They cannot interfere with the donation. That is quite clear, especially recognizing that donation is the most direct form of life-saving mechanism.

However, I differ with Dr. Feldman. I think Halakhah (the law) is the science of the here and now, just as autopsy is. Consequently, I believe it would be a most important step forward. I am never called in to prohibit an autopsy. I'm called by doctors who know that, if the issue is important enough, I will encourage a family to permit an autopsy. There is a big difference if you offer to be present during the autopsy to assure that all conditions are maintained at the highest, most dignified level. You can obtain autopsies that you couldn't get in any other way. Dr. Geller is correct in that, ultimately, the issue is how you teach your students. How are you going to teach interns and residents to respect the human body and please God? When they succeed, there will be no need for anyone else, for each one will be his or her own *mashgiach*. The fact remains that right now an autopsy is a most helpful procedure. Many necessary autopsies for the Orthodox Jewish community are not available—regrettably—because hospital chaplains are often part-timers and are often not available for emotional and psychological support.

Geller: Therefore, because rabbis are not always available, the autopsy permission or request form is a good universal practice to observe when there are no *mashgichim* available or willing to be there.

Trainin: When Rabbi Jacobovitz was chairman of the Federation's Medical Ethics Committee, in 1962 or 1963, we set up a subcommittee on autopsies. We had a meeting with every pathologist in hospitals associated with the Federation of Jewish Philanthropies. At that time, one of the things that our committee suggested was that a rabbi, a qualified scholar, be permitted to attend an autopsy. Perhaps the motion would have passed. But one pathologist objected vehemently. In essence, the heated argument ended the two-year effort to reach some kind of an agreement between a number of top rabbinic scholars and the pathologists in Federation hospitals.

Geller: It is probably not practical for a rabbi to be present at every autopsy. At Mount Sinai, they are certainly welcome to attend. In the case of a highly religious family in which a member dies and the rabbi requests to be present, we would make every effort to accommodate them. I can't recall that happening in 15 years, but we would certainly not impede him.

Question: Considering that man has created the image of God and there are halakhic (legal) problems related to autopsy, what halakhic justification is there for Jewish students to dissect a human cadaver in first-year gross anatomy?

Tendler: In most modern medical schools, anatomy has been so deemphasized it takes up an insignificant part of the education. There are students who go through medical school and become fine physicians without ever having touched a cadaver. In the finest medical schools in New York City, the number of students per cadaver goes up each year. A cadaver is not easily available. The truth is that modern medicine has dispensed with autopsy for the general physician. Certainly you cannot become a pathologist or a surgeon without extensive anatomy training. But the Halakhah is the science of the here and now. It's always important to bring the Halakhah up to the present year. Today, it is possible for a student literally to go through an entire medical career without ever doing an autopsy.

Question: Is it permissible for a government to demand the mandatory donation of organs as Sweden has done? Second, can you tell us a little about what goes on in Sweden?

Greifer: In Sweden as well as in France, the concept that when a person dies, the body belongs to the state is a basic belief. Such a movement is beginning in the United States. Senator Long and a number of others have proposed to Congress that if a person wants to receive Medicare benefits in their lifetime, they should participate in medical donation programs, such as giving blood regularly. It was also suggested that they deed their organs to be used for patients within the system. Basically, we are protected by two laws in this country; one is religious freedom. More important, the Constitution protects each person's right to do as he or she sees fit under the Fifth Amendment. None of us can do anything which we consider harmful to ourselves. Therefore, the proposal was discarded because any such law would be unconstitutional in the United States. A great deal of effort is still being expended by outstanding public figures to promote this idea of organ donation, at least for blood donation. The American labor movement would like to make blood available by demanding that individuals give blood regularly.

Dr. Tendler has appeared before the President's Commission on Medical Ethics to discuss not only brain-death, but many other issues. One issue is, how can a national organ donation system be implemented in law without in any way interfering with individual religious and constitutional rights? One suggested method is through social security—whenever a person signs a social security card or receives annual social security announcements, the chance to sign to donate or opt not to donate organs would be given.

How could a country like Sweden get away with mandatory donation? For one thing, the country is more homogenous than the United States. Of all Swedes, 98% are Lutheran and of the same ethnic group. France, however, has a much more heterogenous population—800,000 Jews, as well as Moslems and Catholics. If a family or an individual doesn't want to donate, they don't do it.

Question: That answers the second part of the question, which was, can Jews accept passive affirmation of their wish to donate or must they take an active position on donation? The answer you give is that not only Jews, but others as well are not very happy with mandatory donation.

Greifer: Many Jews all over the United States, when discussing problems of state laws and regulations, do not understand that anything in the Jewish heritage or Jewish law deals with medicine. In many states, including Missouri, California, Idaho, and Nevada, the state legislature passed laws on such matters without consulting the Jewish community. The Jewish community's answer was that they don't know anything about this. Of the 8 million Jews in America, maybe 500,000 understand what we're talking about. We are taking on a greater responsibility now in trying to teach some of these things. A philanthropist in St. Louis wants to set up a program on Jewish medical ethics. I think pathologists, Jewish or not, should know the code in considering deaths of people of the Jewish faith.

Question: Halakhically speaking, should organs be buried with the body? If one donates an organ which is subsequently implanted in a recipient, when the recipient dies should that organ be returned to the original owner? Is digging up the body permitted to enable the organ to be buried with the body it came from?

Tendler: It is not just that the organ has to be buried with the body. The organ itself has to be buried. Every organ is affected by the same law requiring burial, with the right kind of burial. Burial rights apply to all parts of the body, but that doesn't mean all organs have to be together. It does mean that every organ has to be buried properly, not washed down the drain. If an organ is implanted in someone else's body, it has an independent life, it never died. Therefore, it never had a need to be buried with the first body. Hence, the organ first dies with the second body and then should be buried with the second body. That burial would be proper.

Question: Is embalming permitted? Was not Jacob the patriarch embalmed?

Tendler: Embalming is not permitted. Jacob the patriarch was not bound by the Torah laws which were given to Moses on Mount Sinai. The patriarch lived before that time and followed the code of conduct of Egypt. Embalming is not required by any state or federal law. The idea that you can't ship a body without embalming is a hoax that funeral directors impose on families so that they can charge for it. Nor do you have to send the body in a zinc-lined container which costs $1,100 dollars. As army photographs make clear, a body can be shipped in a zippered plastic bag and meet all legal requirements. Embalming is looked upon as a desecration of the body in Jewish law. There is no point to it since the resurrection of the dead will involve a far better preservation of the body than embalming fluid can perform.

Question: You have been discussing permission to donate organs prior to death. Is any person permitted to donate his or her own body prior to death for dissection in the anatomy laboratory?

Feldman: Biblical law requires that the body be buried with proper burial rites. A person cannot waive that, cannot say don't bury me, cremate me. What a person can say is, don't bury me, use my body to save a life. Use it in accordance with Torah law to help somebody save someone's life. Use my body for dissection. The dissection is not in vain, but it is for a good, life-saving purpose. Anyone can donate an organ, or can decide not to donate an organ. The only thing no one can do is desecrate the body by embalming, by unnecessary cuttings, by unnecessary cremation. No one can will their body for anything but a Torah-sanctioned purpose.

Question: Dr. Tendler, you stated that one may not forfeit one's life to save someone else's. Although no one is obliged to, if someone wants to be heroic and save another life by sacrificing his own, he may do so. There are both early and late halakhic authorities who have so decided, such as Rabbi Kook. Could you clarify?

Tendler: There is the early, famous controversy between the Babylonian Talmud and the Jerusalem Talmud in the case of risk. In the case of significant risk, must you or may you risk your life? I know of no reputable authorities that permit sacrificing your own life for somebody else. The only circumstance under which that rule doesn't hold is under the unique circumstance known as warfare. Warfare has its own moral ethical principles that are not relevant except during warfare.

Question: What is the criterion to use to determine whether a patient truly agreed to a postmortem removal of organs while still alive? Signing a donor card? Is that sufficient?

Tendler: What would be adequate is someone of integrity saying, "He told me so." We would not question it, nor does it require an opinion. Can you read into anyone's lifestyle what they would have said under certain conditions? Because of the nature of the gift, namely its life-saving potential, certainly we would take a more lenient approach on how we determine volition.

Question: Can a deathbed wish be accepted halakhically for organ donation? Does a witness other than a doctor have to be present?

Tendler: We trust doctors. We don't require that the team that does the transplant should not be the one that declares the donor dead. We accept the integrity of the physician. Testimony by a physician that the patient made such a wish would certainly be acceptable. A deathbed wish has the greatest halakhic validity.

Question: In the case of a homicide victim, autopsy is required to retrieve the bullet to convict the murderer. If this victim is Jewish, is an autopsy permitted?

Tendler: Unfortunately, nobody asks that question in practice. When autopsy is required, the coroner does not listen to any kind of religious objections. This is one of the legal requirements. No leniency has ever been allowed—they will always do the autopsy. If you can exonerate an accused criminal by doing an autopsy on the victim and show that the accused's act did not kill, then you have saved a life in court as well as saved a hospital bed.

Question: Is it true that doctors receive monetary remuneration for organs they obtain for transplantation?

Greifer: Under the law, they are not supposed to. As far as I know, this is not even a general condition in the United States. Many years ago, residents were given presents for getting permission for an autopsy for organ donation. I knew about it on two occasions. We discussed it with the people involved and that type of thing was stopped. In general in the United States, there has not been any exchange of any kind of gift of value between donor and recipient. If it is done, it is done quietly, under the table. It is not done, nor has it been accepted, in the open, nor has any person in the United States supported such an act. In fact, the group as a whole has believed it would be highly unethical for hospital or surgeons to transplant when they are aware that an exchange has occurred. There was a question about whether a family could sign permission for the kidneys to be taken from someone who has just died. It is very important that if the tenor of feeling in the family is receptive to donation, donation is not ruled out. Similarly for children under the age of 18; any legal document signed by someone under 18 has no value, but if the family believes in transplantation, or does not believe in transplantation, you can reasonably assume that the child would believe the same thing as the parents. The question then is would a family have the right to allow a 15-year-old's kidneys to be given for transplantation if that was the choice of the family?

Tendler: Yes.

Geller: The issue has been raised several times about the satisfaction of doing needle biopsies or peritoneoscopy rather than complete autopsy. From the vantagepoint of the pathologist, such procedures are often to no avail. The complete autopsy supplies the answer whereas needle biopsy often does not, simply by the limitations of taking a tiny little piece of tissue. Wouldn't it be a desecration of the body to seek an answer to a problem and then to engage in a practice that will not, in most cases, answer the question?

Tendler: The assumption is that the needle biopsy is used only when the pathologist feels he or she will get an answer; otherwise there is no point in doing it. But you must realize that the basis of the principle is that "defiling" must be defined. The principle is based on the procedures—nonheroic, ordinary—a patient undergoes while alive; such procedures cannot be classified as defilement. Liver biopsy or kidney biopsy have been accepted by society as nondefiling. That is the basis of the principle.

Question: If someone dies of a totally unknown cause, is an autopsy permissible to detect the cause? Also, a person buys life insurance to provide for his or her family. If the insurance company refuses to pay without an autopsy, may one assume the consent of the deceased? May an autopsy be performed under the best of conditions?

Tendler: I've dealt with that twice this year. In one case, they wanted to determine whether the death was suicide or accidental, and wanted an autopsy for that reason. In both cases, we ruled against autopsy. In both cases the family approved the autopsy. They approved it because of the insurance policy. They wanted the money, but the question was posed to the rabbis, who answered; then the family decided on the basis of their best interest.

Question: Is there any law about this?

Feldman: It doesn't come into the existing categories allowing autopsy. It's not saving life in court or in the hospital. It's only saving money, so it doesn't fall into any of the permissible categories.

Right to Know

Gribetz: The Federation committee, rabbis and nonrabbis, finds a consensus. That is, we are not supposed to make unilateral decisions. Dr. Butler, for instance, is spending most of his professional career on this problem and has written a book about it. The National Institutes of Health have been wrestling with this complex problem as well. Apparently, there seems to be a difference of opinion—the utilitarian theory versus what is called the deontologic theory. Namely, do you tell the truth to a patient? Can you do so without fear of doing the patient harm? I think you must tell the truth no matter what. Dr. Butler, what is your reaction?

Butler: I am reminded of the character in Ibsen's *Wild Duck,* Doctor Relling, who constantly goes around telling people the truth about themselves. First of all, his "truth" is the truth as he sees it, which may have its own biases. Secondly, who asked? The right to know, per se, does not mean that you insist on telling the patient, or anybody, everything. You should be responsive in an appropriate personal, ethical, humane way when the person asks or appears to want to know. Judgment and mutuality must be used in determining the degree of truth and the timing of expressing such a truth. For example, does that person have or not have cancer? Do they or do they not have a good prognosis? As Rabbi Gordon pointed out, there may be a natural time for truth to be expressed. This is the point of the Ibsen play. The brutality of truth can destroy the necessary illusions that a person must possess.

Care of the Elderly

Question: What is the Jewish view of children who place their parents in nursing homes? Does this constitute abandonment? Is one thereby violating the Fifth Commandment?

Gordon: The basic Jewish view as described in the Talmud interprets the Fifth Commandment, "Honor thy father and thy mother," by ruling that the obligations of children to parent involve feeding, clothing, sheltering, and taking care of immediate needs. How should this be done by a child or a surrogate? At whose expense should this be done—at the child's expense or at the parent's expense? For example, a very wealthy parent with a miserly disposition has amassed millions but has shown no love to a child. Knowing the child is religious, the parent at age 70 says, "I don't know why I should pay rent anymore, or why I should buy my own food or pay my bills. You have an obligation to support, feed, and shelter me. You are religious. You abide by the Fifth Commandment. I'll send you my bills each month. Take care of me." The Talmud says the child is obligated to take care of the parent's needs but not necessarily at the expense of the child if the funding is available from the parent himself. In my rabbinic career, I have seen situations in which placing a parent in a nursing home was really abandonment for the craziest and most selfish of motives. But I know of many more cases of children placing a parent in an old-age home clearly and objectively for the best interest of the parents. They received the most constant and permanent care, and placement may very well have avoided what could have been a marital breakup in the home where the parent was living. That's also an ethical consideration. Therefore, I can't give a yes or no answer.

Butler: I concur. Nursing homes and homes for the aged have a necessary place in the care of older persons. However, the quality of homes, nationally, is something that we as children of the elders of our culture have much to wonder about. Some 50% of American nursing homes cannot even meet minimum fire standards or minimum sanitation needs. Ninety percent of the care is conducted by nurse's aides who frequently are performing their jobs as a kind of coerced philanthropy. They have not been adequately paid. They are usually at minimum wage, with a 75% annual turnover. Our culture, not just individuals, has some questions to ask of us. How do we care for our elders? From a purely self-interested point of view, if we think there is a link between our present self and our future self, we had best ask that question. Finally, 50% of people in nursing homes have no family. Seventy-five percent are women who have outlived their husbands. We have a special obligation and concern for the lives of our women.

Tendler: Dr. Butler mentioned earlier the drop-off of visits at nursing homes. The talmudic reference Rabbi Gordon made says the responsibility of a son or a daughter to feed a parent means just the same as our responsibility to feed an infant. Physical ministration is the main obligation of a child to a parent. Monetary considerations are strictly the parents' obligation unless they are without funds. Then it falls into a special category. The job of feeding means being there for breakfast, lunch, and supper, making sure of the physical care of the parent that cannot be relegated to anybody else. Justification for putting a parent in a nursing home then would only be under ideal conditions, which Dr. Butler has not been able to confirm to his (or my) satisfaction—that nursing homes in America are fully cognizant of the *mitzvah,* the good deed, they do, in those instances when a parent cannot be properly cared for at home.

Who Should Decide?

Question: Dr. Tendler, you said in your presentation that the decisions in relation to an infant couldn't be made by the parents because they weren't able to, decisions should be made by medical personnel in emergencies. The idea of a surrogate to handle decisions objectively is an interesting one, in halakhic terms—a friendly, objective, informed decision-maker who is not one of the parents.

Tendler: The parents' ethical role is not understood in biblical literature the way we understand it now. Somehow, our society has given parents more rights than they deserve. The rights of decision-making in basic issues are not the rights of parents. They are the rights that come from our ethical system. The one best able to understand, explain, and administer ethical decisions is the one who is responsible. A parent has no greater responsibility for the son or daughter than the responsibility which is vested in him or her by biblical ethics. If the parent is ignorant thereof, he or she doesn't function as a parental authority, but functions by what Rabbi Feldman mentioned—putting a "stumbling block in the path of the blind."

Question: Dr. Butler, with the elderly, you run into the problem of their not being mentally able to evaluate the information and choices they are faced with. Who makes the decision if they are incompetent—the doctor, the social worker, or the children?

Butler: First of all, the bulk of older persons are perfectly competent. Even those in nursing homes have a high range of competence. Furthermore, there is a continuum for competence. Competence to do what? Specific matters of law bear upon whether the person understands the natural disposition of their goods, making arrangements for legacy. Be careful in forwarding the impression that the vast majority, or even the majority of elderly persons, have any mental incompetence. Of those that do have, then you have to ask this specific question: Is incompetence related to contract? Is it related to testamentary capacity? A combination of medical (usually psychiatric) and legal authorities together help to participate in that decision-making process.

Why has nobody mentioned the contagious courage of the doctor as a strengthening factor for patients in difficult situations?

Physicians and Contagion of Courage

Gribetz: Let me extend that question, because it is something that has bothered me for many years. When a situation is probably desperate, after giving parents the facts as best I can, am I right or wrong to leave them with a ray of hope, even if it is not a realistic ray of hope?

Gordon: "Contagion of courage" is a good metaphor. I spoke of the asymmetry of power, and the trust a patient who may be vulnerable and ill puts in a physician, and spoke of the doctor providing life-support systems through alternative suggestions, other scenarios. Clearly the role of the physician, and for that matter the role of anyone else in contact with the patient, is to give courage, strength, fortitude.

Question: Another question about allowing the hopelessly ill and the pain-ridden patient to die. Is there unanimity among the panel that an act of omission is morally distinguished from an act of commission?

Gordon: Is an act of omission the same as an act of commission? No, of course not. There certainly is a time when not to treat. Not to treat means omission. There is never a time when you hasten death by an act of commission, not by our ethical system. Certainly the parameters of not treating are far more complex than time permits us to answer.

Tendler: There is a difference between a hopelessly ill patient and a pain-ridden patient in Jewish ethics. The pain-ridden patient, if there is no other palliation, is more likely to fall into the category of when not to treat than is the patient who is comatose but feeling no pain.

Incompetence and Rights

Question: What are the ethical dilemmas in regard to the mentally competent yet physically deteriorating patient who wishes to return home from the hospital? Family or physicians may feel home is an unsafe environment, even though the patient may face the first of the two deaths in an institution.

Butler: The patient's request has to be honored, period. If they wish to go home, they can go home.

Question: Isn't there an ethical dilemma for the child who knowingly sees a parent going into what he or she perceives as an unsafe situation?

Butler: For instance, an old woman lives in a deteriorated neighborhood. She could possibly be threatened by breaking and entering. The filial responsibility of the child to ministrate to parents permits the child to overrule the parent in regard for the parent's own safety and welfare. One would have to know a specific patient's history. Presumably, the patient came from this place and had been surviving. Now the patient has asked to return to this place. If the children want to make an offer to help enhance the environment, they should discuss that with the parent. It would be extremely gratifying. The parent might decide to respond to the wishes of the children or might not. But it still would be a decision by a mentally competent person, a decision that would reside with the patient. The question might arise, of course, how they had lived under such circumstances to begin with.

Tendler: Dr. Butler mentioned that senile dementia is a significant problem in the aging population. What kind of volition remains, what are their rights? In one case, a loving couple, the wife took care of her husband, who had Alzheimer's disease, for ten years and finally had to put him in a nursing home. During those ten years, the husband pleaded to give his wife a Jewish divorce which would allow her to remarry. After he had been in the nursing home for a few years, an opportunity for remarriage presented itself to her. She wanted to take advantage of what she was convinced were her husband's wishes. Yet he was totally incapacitated. By Jewish law, you cannot give a divorce unless the husband expresses voluntary consent. The medical people were convinced that he was totally incapacitated mentally. We called in a polygraph expert. We were satisfied by religious law that this man was responding, even without being able to blink answers. We convinced ourselves that he was indeed participating intellectually in his environment and that his main interest in life was to give his wife a divorce. She was granted a divorce on that basis.

Butler: I admire your enthusiastic approach to the problem. Probably, if we could have retrospective presentations of what a person's wishes were during the period of that person's lucidity, we would have a more ideal approach. Certainly the degree of physical brain change can be so profound that the probability of such a clear message being sent would be very much in doubt. Again, remember there is a continuum of competence and, in some measure, you may indeed have been properly assessing the wishes of that person.

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IV. Triage of Scarce Resources

Triage: From Government to Institutions

Thomas C. Chalmers, M.D.

In the difficult times to come as technology in medicine advances, it will be ever more difficult to maintain entirely ethical practices. But we in medicine must maintain the highest possible standards and do all we can to achieve them. Browning said that a man's reach should exceed his grasp, or what is a heaven for? I believe that in the practice of medicine one has to have ethical goals to strive for, and the responsibility and charges to the people who operate the medical resources of the government should be just as ethical in aim.

It seems to me that the ethics of the individual practitioner of medicine cannot be separated from the ethics of the local administrator or the bureaucrat who is making decisions in Washington about the distribution of funds for medical care and research. Both have to think in terms of the responsibilities of the individual physician when they put together programs and allocate scarce resources. To be sure, societal ethics necessarily differ somewhat from those of the individual, but to whatever degree we rank societal ethics ahead of the individual, we're in trouble. In planning how the government is going to appropriate scarce resources, we must start off with a code of ethics related to the individual.

My own personal medical ethics, in order of importance to me, are as shown in Table 1.

The Interests of the Patient

The greatest source of unethical behavior by physicians, medical students, doctors in training, or doctors with years of experience is ignorance. That is the one quality that physicians must avoid above all else if they are to practice ethical medicine. They can't make a patient suffer because they are ignorant of a recent advance or a traditional rule, or because they are not as knowledgeable as they should be in the care of the individual patient. The bureaucrat in Washington, the person who is dispensing money, who is proposing to Congress how money should be spent, is also hampered most in arriving at the most ethical decisions by ignorance of medical science, sociologic need, and the state of the art of the practice of medicine in the country.

The second ethical sin is one which the individual practicing physician must particularly guard against. Personal greed, which does not necessarily have to be conscious and can be increasingly subconscious as one grows older and acquires more personal financial needs, has to be watched for when striving for ethical practice.

There are other sins. Dogmatism—we've all seen our peers fall into the trap of being dogmatic about patient care and, therefore, closing their minds to medical advances or the opinions of others. Consider the position of the government worker who is dispensing money to institutions; dogmatism there can be a great danger. Pride may operate at both the individual and government level and can only be countered by intellectual honesty. Sloth as an ethical sin is I think self-explanatory. It may be a bigger problem in Washington, where there is no fee for service.

Last in this list is protection of the research subject, sick or well. Because biomedical research in which physicians treat patients as part of a research protocol is the only kind of patient care that requires elaborate informed consent and detailed peer review, it is much more ethical, to my mind, than the practice of medicine. Rare episodes of mistreatment of research subjects have resulted in an elaborate mechanism for their protection,

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TABLE 1
Medical Ethics: The Golden Rule

Problems	Solutions
The Patient's Interest	
ignorance	scholarship and research
greed	moderation in all things
dogmatism	fairness
pride	intellectual honesty
sloth	responsibility
anomie	responsibility
protection as research subjects	peer review and informed consent
The Family's Interest	
dying and death	compassion without lying
geriatrics	traditional responsibility
abortion	individual choice
infection and toxins	education
finances	ingenuity
The Community's Interest	
contagious diseases	reasonable isolation
expensive diseases	research and ingenuity
geriatric medicine	a community responsibility
Humankind's Interest	
health of present and future generations	the human concern
nuclear war: the last great plague	education

one that has placed an increasing wedge between clinical research and clinical practice. When a treatment has not been established as efficacious, for example a new use of an old drug, it is easy to try it out in a few patients. No peer review or detailed informed consent is required by any government agency. But the physician who wants not only to treat the patient well but also to find out whether the innovation works must go through an elaborate and discouraging process. So, not enough clinical trials are carried out.

Government Influences on Medical Ethics

In a sense, the government has projected itself partway into the ethical practice of medicine by requiring peer review and elaborate informed consent before a patient needing treatment can be placed in a randomized control trial. There are other much more indirect ways by which—through the financing of medical care—the government is influencing the ethical practice of medicine. Examples will begin to pile up as more and more technologic advances need to be paid for. Consider two contrasting examples, long-term renal dialysis and coronary artery surgery.

When the technology became available to keep patients with renal failure alive indefinitely by dialysis two or three times a week, no randomized control trial was necessary to establish efficacy. But nephrologists found themselves in a triage situation. Limited facilities and manpower meant that some patients, those less rehabilitable and, to a certain degree, those less able to pay, were allowed to die. Then the social security laws were amended to fund the treatment of renal failure. Physicians were rescued from an untenable ethical position. They no longer had to do any triaging that was not in the best interests of their patients.

A different example of government-physician ethical interaction occurs in coronary artery surgery. Because the patients undergoing such surgery tend to be middle-aged, previously healthy, and working, private insurance is a more important source of funds than for dialysis. The annual costs have risen to $1–2 billion, compared to about $2 billion a year for chronic renal dialysis. Few ethical problems of triage arise in coronary artery surgery. But another kind of ethics is involved: the squandering of limited healthcare funds by the overuse of an expensive form of treatment.

Although clinical experience suggests that surgery relieves incapacitating angina more often than does medical treatment—and in some cases brings about objective improvements in cardiac function—randomized control trials have shown that life is prolonged only in those with left main artery obstruction and those with triple-vessel disease and some ventricular dysfunction. There is no evidence that life is prolonged for those with one- or two-vessel disease; especially is there no such evidence for asymptomatic patients who have had a myocardial infarction or flunked a stress test. The figures are hard to come by, but it is possible that up to half the operations performed in this country are done on patients whose disease has not been shown to benefit from surgery. They might do just as well on modern medical therapy.

If unnecessary operations are unethical behavior, then ignorance and greed are leading to the wasting of a lot of healthcare resources. The situation could become a lot worse as more and more complex and expensive technologies become available for routine use before they have been established as both efficacious and safe. Balloon dilatation of obstructed coronary arteries and intra-arterial injection of streptokinase are good examples. Other examples are plasma exchange and removal of possibly offending white blood cells in diseases of unknown etiology, such as lupus erythematosis, rheumatoid arthritis, multiple sclerosis, and myasthenia gravis. Is it ethical to employ these procedures routinely before their worth has been proven?

Third-Party Payors: Research vs. Healthcare

The government and other third-party payors are involved in this ethical problem because they have the means and the funds to require adequate evaluation of each procedure before it is misused. There have been some instances of refusal to pay for unproven innovative procedures, but this has occasionally carried over to patients who are part of controlled trials. There is a growing feeling that research rather than healthcare funds should pay for the trials. Yet this raises an ethical problem of direct concern to government. Should money available for basic research be diverted to finance the ever-increasing number of clinical trials required by advancing technology? Should the health of future generations be impaired by the diversion of basic research money to the benefit of those now sick? That's an ethical dilemma for the government.

There is an obvious solution. Third-party payors should refuse to pay for innovative therapies and expensive diagnostic procedures unless the procedures have been shown to be relatively beneficial and safe. But, at the same time, third parties should pay for the treatment of patients who are included in randomized control trials designed to determine the relative efficacy and toxicity of innovations. That would be an ethical way out of an increasingly serious healthcare problem.

This funding proposal would actually save a lot of money. It is likely that many new procedures will not prove efficacious, and definitive trials would be a lot less expensive than routine payment for the procedures. For instance, multiple trials to determine exactly which patients do benefit from coronary artery surgery could be conducted for under $50 million a year. That is a lot less than the hypothetical $500 million that is now being wasted on unnecessary and occasionally fatal operations.

There is much talk of the need to cap healthcare costs at 10% of the gross national product. That goal will not be attainable. The increasing availability of expensive technology and the increasing proportion of old and disabled people, kept alive by some of that technology, will increase costs far beyond what can be saved by increased efficiency applied to our present methods. Physicians will again be forced to triage, as they did with chronic renal dialysis. In fact, the British are already capping costs by forcing physicians to let some patients die because the resources are not available to keep them alive and relatively well. Patients with renal failure who are over 65, no matter how healthy they might otherwise be, are excluded from long-term dialysis unless they are rich enough to pay for it privately.

If the U.S. government insists on capping costs at 10% of the GNP or substituting a competitive system of healthcare, physicians are sure to be plunged into ethical crises of the triage kind. To be sure, they already do make life-and-death decisions, but these decisions are ethical because they are based solely on estimates of the probability of recovery. If they are also based on cost, they will be unethical. So the government must find ways to reduce costs by forcing proper evaluations of healthcare practices in order that physicians will not start down the slippery slope of withholding known effective remedies because the funds are not available to pay for them.

The slippery slope will resemble the one described by Leo Alexander (1) in his study of German physicians during World War II:

> Whatever proportions these crimes finally assumed, it became evident to all who investigated them that they had started from small beginnings. The beginnings at first were merely a subtle shift in emphasis in the basic attitude of the physicians. It started with the acceptance of the attitude, basic in the euthanasia movement, that there is such a thing as a life not worthy to be lived. This attitude in its early stages concerned itself merely with the severely and chronically sick. Gradually, the sphere of those to be included in this category was enlarged to encompass the socially unproductive, the ideologically unwanted, the racially unwanted, and, finally, all non-Germans. But it is important to realize that the infinitely small wedged-in lever from which this entire trend of mind received its impetus was the attitude toward the nonrehabilitative sick.

So the government has been, is, and will be involved in the ethical practice of medicine, and the principles involved are pretty much the same as those faced each day by the practicing physician.

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Triage: From Institutions to Departments

MARTIN S. BEGUN

I will be forever grateful to Dr. Donald Gribetz for stimulating me to give serious and prolonged consideration to the impact of ethics on the day-to-day operations of the dean's office as well as the philosophic underpinnings of its functions and objectives. The place to begin is a look at the process whereby decisions are made. Only then can we speak of ethics as they relate to the allocation of funds, scarce or otherwise.

The power in an academic medical center is basically in the hands of its faculty. At the same time, however, such a medical center is an institution of autonomous professionals who are pledged to practice medicine by applying their expertise for the good of their patients. A 1981 article (Schwartz WB. The regulation strategy for controlling hospital costs. N Engl J Med 1981; 305:1249) addressed the physician's obligation to his or her patient and, in light of this, questioned the wisdom of asking the physician to set national or institutional priorities.

A physician must do all that is permitted on behalf of the patient. In this sense, the obligation of the physician/scientist and the dean are complementary but not identical. Although the authority of the dean and his associates is derived from the faculty, the purpose of the dean's office is to arrive at institutional judgments. Therefore the ethics of this office encompass those that are specified in the Hippocratic oath, but also extend to the realm of management and governance.

The dean is probably best described as the first among equals; selected by his peers, he is the chief executive officer whose managerial strength emerges by virtue of the confidence which department heads and faculty members exhibit in his ability. Since the real power resides in the school's faculty, the dean simply harnesses this power to the needs of the institution by virtue of his abilities. The dean and his associates are to be flexible, to provide leadership, to form coalitions, and to represent a consensus within the faculty. In a sense, the dean acts as a referee. His strength resides in his ability to mold the interest and to develop a group identity. When making choices in the allocation of resources, his purpose is to avoid destructive factionalism and to maintain the common goal of the institution as it has evolved over the years.

Peter Drucker points out, in his pivotal book on management, that the skills of a manager or of a dean are those of negotiating compromise, mobilizing energies, and—above all—setting priorities. Total objectivity is clearly impossible to achieve. For this reason, the dean's office is frequently the butt of attack from an academy whose stated purpose is the pursuit of "truth."

How, for example, are we to choose between funding a potential Nobel laureate as opposed to someone who is engaged in research which promises immediate and practical results? How is risk to be weighed against certain outcome? Decisions such as these are often made on the basis of what I like to call "institutional personality." Every medical center has its own personality, as does every university, and these personalities differ from one institution to another on the basis of goals and objectives as defined over time by the faculty and by the trustees. In determining policy and allocating resources, the institution as an entity, with its history and distinct interests and goals, is given primary consideration.

The dean's responsibility is to the institution as a whole—not to a department, not to some individual faculty member, but to the institution as a whole. In that sense the dean also represents society.

As the chief executive officer, he is accountable to the public at large for decisions that have been made by the faculty collectively and individually,

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and by the dean's office. Decisions such as these are often made on the basis of institutional personality and provide the criteria for evaluating the success or failure of the institution in meeting its goals. The institution's performance of a specific mission is also society's first need and interest. Society stands only to lose if the performance capacity of the institution, in its own specific task, is diminished or impaired. Hence, performance of its function is the institution's first social responsibility. When allocating resources, therefore, a balance must be maintained between satisfying the interests among various groups and reenforcing the image which historically has been a part of the institution. Throughout, however, we must bear in mind the underlying professional responsibility that is a part of every physician's ethics as incorporated in the Hippocratic oath: *Primum non nocare,* "Above all not knowingly to do harm." This is the first, basic rule of professional ethics as well as the basic rule of an ethics of public responsibility.

Thus far, I have referred to Drucker's comments to indicate the similarities between the position of dean and that of the manager of any business enterprise. But differences do exist between academia and business. These differences should not be ignored, especially since they have a direct impact in today's economic climate, when cuts in government funding have resulted in increased cooperation between the medical centers and private enterprise. In spite of all efforts at regulating this relationship, problems are certain to arise, and questions of ethics and accountability must be addressed with honesty.

To what extent do the values of the marketplace apply to the laboratories and lecture halls of the university? In the age of genetic engineering and rapid progress in all the biomedical sciences, this doubtlessly will pose ethical questions that are both timely and probing. Additional questions will certainly result from a government whose change in attitude has brought enormous strain within the public sector—causing the need for a reordering of priorities and a redefinition of objectives.

Decisions will be made and priorities will be established on the basis of all the factors listed above—the faculty, the institutional personality, and the needs of society.

At the center, however, is the one individual who is responsible to the entire medical center, and not to any one faculty member or department head. The position of dean has evolved gradually over the years as academic medical centers have expanded and grown increasingly complex. The dean's office will continue to evolve in the years ahead, and the transformation in its aims and objectives will be publicly debated, as will be the corporate and business ethic when together they confront a world of limited resources and extensive economic and social commitments.

The question essentially is one of decision-making. When you look at the medical centers in New York City today, you must take into account their enormous responsibilities for patient care, education, and research. Institutions of this size and dimension are constantly in a position of making choices—and the dean's office is at the center of these decisions. The process whereby judgments are made has proved to be effective and has certainly been responsive to the ethical issues of a profession which has never been static. Our role as members of offices of the dean is to assure that the decision-making process remains responsive to a variety of factors so that academic medicine will continue to meet ethical challenges in the years ahead.

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Rabbinic Comment: Triage of Resources

Rabbi Moshe D. Tendler, Ph.D.

Perhaps the most difficult aspect of the very difficult problems we face in discussing triage of resources is that no one has had much overt instruction in the classic literature. Not that triage issues were ignored in the past; but society has become so complex in the course of the last five or six centuries that the divisions under which we are discussing triage here—national, international, departmental, institutional, the individual patient—represent divisions that never were as clear, never were as distinct as they are today.

The question that I'd like to ask is: Do the same axioms of ethics apply to institutions, to society as a whole, as to individual decisions? The problem is well known in the microbiological, pharmaceutical, and chemical manufacturing industries. It is the problem of scale-up. As everyone who has worked in microbiology knows, a bug can behave very well in a 10-ml broth in a test tube. Researchers move it into a 100-ml flask, and if they are lucky the bug still behaves. If they are really lucky, the bug still behaves when they put it into a 7-L fermenter. But when commercial firms evaluate initial results, they don't play around with a few liters. They throw the bug into a 500-gallon vat for initial evaluation. Suddenly the bug lays down and dies. It doesn't do a thing. It's supposed to put out a good enzyme, a good antibiotic, maybe a good antitumor agent. But it lets the researchers down. Quantity is, in itself, sometimes a qualitative issue.

Triage at the societal level is conflict of goods. No one involved in medical triage is choosing to kill one patient and save another patient. When the decision is made in an institution not to order more intensive-care beds but rather to fund a well-baby clinic, or to push more money into a screening program, nobody is out to kill anybody. I'm not choosing to offer water to one man walking in the desert over another man walking in the desert. Therefore, the moral turpitude that is involved in a life-or-death triage decision is not there. Sometimes the amorality of the decision becomes very obvious. There isn't that compelling need to make the decision when no eyes stare at you, no family batters you with questions. Without that psychological stress, there is a greater tendency to lean back and make decisions using standards that have yet to be defined.

Triage: One Good against Another

A decision between basic research and applied research is a problem we in medicine have been living with all along. People in active research have no doubt that they must get more money for basic research. And without basic research, the future holds little. Yet the medical practitioner, the administrator, the ethicist realizes that if the money goes for basic research, there will not be another dialysis machine.

The infinite worth of all humans is the basis of our Western ethical system. But our society has only finite resources, and once those finite resources are revealed, the infinite worth of each man and woman suddenly has to be discounted to bargain prices. Somebody must make the choice in the war of the goods, one good against another.

Esthetics versus Technology. Let's push the idea of good versus good a little further, to include the war between esthetics and technological improvement. To run an opera house costs money. To run our museums costs money. What right do we as a society have to invest money in a museum of modern art or in a museum of natural history which contains such things as dinosaurs and imaginary missing links? What right do we have to support these institutions at the cost of another intensive-care bed? I have a son who is in medicine. During a period as chief resident, he

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regularly had to choose which patient got the ICU—the intensive-care unit—bed. There aren't enough ICU beds to cover all the patients coming out of surgery. There aren't enough ICU beds to cover the demand of every surgeon who wants his patient to get the best care. Yet some young physician, a year or two out of medical school, must make decisions on the basis of rules established by someone, someplace. Why should he have to make that decision? Why didn't someone provide him with two, three, or four extra beds, more than he could possibly need during the entire residency program?

My personal peeve—and I know it is a personal peeve because my son the doctor told me so—is that I travel down the Palisades Parkway in New Jersey every day, and virtually every day on that route I watch a two-cylinder lawnmower at work mowing the lawn the entire length of the parkway. Whenever I see that lawnmower I ask myself who made the decision that the lawn should be mowed and that the ICU bed should not be provided. Here we're not choosing so much between one good and another, between more ICU beds, a well-baby clinic, or more money for a geriatric program. This is pushing into the area of social luxuries. Why must the Palisades Parkway look nicer than my own lawn?

Society as an Entity

Such decisions are being made at a societal level. Is it now the rule that society makes its decisions amorally, without needing to take into account the triage problems that are being faced by every individual in society? I ask you: Is society an entity such as a corporation, a limited liability company? Is it a new entity like a corporation that is neither the president nor the vice president (who happen to be married), nor the treasurer (who is their son), nor the secretary (who is their daughter), so that when these four people steal from the stockholders, they remain pristine pure but the company is in deep trouble? Is there such an entity as "society" which as a gestalt is more than its component parts?

I'd like to suggest that, indeed, there is. Societal ethics are more than individual ethics. Whereas individual ethics must be taken into account in societal decisions, there is more to society than the individuals in it. Society means governmental control. Society is governed by regulations and expectations. In Jewish tradition, the Jew in exile is ordered to pray for the welfare of his government; "if not, man would swallow his fellow man alive." Government per se serves a function: to establish a social milieu that protects the values that the society cherishes. The question, therefore, is, Can social values circumvent the basic axioms of the ethical system upon which Western civilization is based? Western civilization is based on biblical ethics. The key to biblical ethics is the infinite worth of the human being.

Anatomy of a Talmudic Discussion: Kidnapping. I would like to open up a line of reasoning which is peculiarly talmudic or rabbinic, and present the anatomy of a responsum. How do we Jews go about evaluating a new idea, a new concept, a new question, such as the one posed: Is society bound by the same ethical considerations as the individual? What does the Talmud, the repository of Jewish scientific ethics, teach us?

"Scientific ethics" means ethics that have withstood the test of time. An ethical system that has survived unchanged for three thousand years can claim to be a scientific system, and biblical tradition has been tested in different societies at different times and not been found wanting.

The Talmud records opinions on what was once a constant problem, kidnapping, which has unfortunately been recurring. Ransoming captives is now as regular an occurrence in Argentina, for example, as it was in ancient Israel. All over the world businessmen have to drive around in armored cars and post guards at their doors, for fear of being kidnapped. The Talmud rules that paying an "exorbitant" amount of money to redeem anybody is forbidden. (Some authorities interpret "exorbitant" to mean "more than he's worth on the slave market"; in the days when slaves were sold, as they still are in some countries, quotes on the dollar value of, say, a six foot, 200-lb, 25-year-old carpenter were always available.) The talmudic approach is, If they want a million dollars ransom, let them go jump; they'll kill him, too bad. The Talmud explains this fatalistic attitude in two opinions, one based on the reasoning "lest society be impoverished," the other on "lest ransom encourage the kidnappers to increase their attacks." The first line of reasoning is that society can't afford ransom—if we were to ransom these people, we won't have money for other social needs and, therefore, we can only extend our sympathy. It is a classic triage. The second line of thought is that if the ante for kidnapping is high, people who never thought of kidnapping would start—if you can get enough money robbing banks, who has to work?

However, the Talmud says that a husband can redeem his wife at any price and a father can redeem his son at any price. The underlying meaning is that no one can establish an ethical principle that compels society to pay any price to redeem a captive, and society can survive such an ethical decision to forgo ransoming someone. But a husband has a duty to his wife to redeem her at all costs. A father, if he can afford it and wants to do so, may redeem his son at an exorbitant fee. Ethically, he can't be stopped from ransoming, because basically he is doing what is ethically correct. He says that money doesn't count when it comes to saving a life. Here you see a clear distinction between a societal ethical decision and a private ethical decision. Society needs money for other expenditures.

The Talmud underscores that there is no greater *mitzvah* (good deed) than ransoming someone who has been captured. Surely it is a *mitzvah* to feed the hungry and the thirsty and clothe the naked? Someone who is a captive has all these needs combined. Redeeming him is a multiple *mitzvah*. Yet society is forbidden to spend an extra dollar. Society cannot afford it.

The concept of relative needs in society is developed in a second example in the Talmud. A town on a hill was successful in digging a well and had adequate water for its physiologic needs. But in a town further down the hill, the inhabitants could not drink water unless the people above refrained from laundering their clothes. There is moral obligation on the town above to provide water to both towns; you can't let the other town die, you are required by law to provide them with water. If there isn't enough water for both towns, the one town drinks and the other town better move elsewhere, quickly. If, however, there is enough drinking water for both towns provided the higher town does not wash its clothes, the Talmud rules that the town above should wash its clothes and not provide water to the lower town. Why? Because in the long run, it is impossible to survive without washing your clothes. The immediate danger is to the lower town. The long-range danger affects both towns equally. Typhus would certainly decimate the higher town in time if no one washed their clothes.

Time Scale for Decisions. Now here is a brilliant insight that helps define my premise. Society differs from the individual in the time scale that society uses for decisions. An individual responds to the problem at hand. Society has a long-range view. Society must deal with the future of itself, with its own survival. Of course, each individual should worry about the future of society, but the individual's decision-making process concentrates on the here and now. This long-range view which must be taken by society is the basis of contractual relationships. This is why society can contract to indebt your children's children's children by thousands of dollars. They are born indebted. What right did my grandfather have to put me in debt? His societal decisions are binding on all future generations because he is responsible for future generations.

Triage decisions are made between two communities—I have water, you don't have water. They are made between two departments—who gets the allocation of funds? But triage decisions between our generation and those yet unborn must also be made. A classic case of intergeneration triage is just now developing. We can switch on the plutonium technology, but even with all our technology, we don't yet know what to do with the radioactive waste. The heck with it, we can put it in cement cannisters, dump it in the ocean. We have enough technology now to hide waste certainly for five hundred years. But what happens after that? What about the yet-unborn generations? After five hundred years, how many people will get leukemia and how many will have malformed children? Whose concern is this? Do triage concerns extend to other generations? Of course they do.

A famous haggadah (allegorical tale) in the Talmud describes an encounter between a righteous man and an elderly farmer planting a carob tree. In botanical tradition, the carob takes seventy years to produce fruit. The righteous man say, "Why are you doing this? You won't eat of this fruit." The farmer answers, "I found the carob tree because my great-grandfather planted it. I will leave it for my great-grandchildren."

This responsibility to future generations should be the basis of personal decision-making as well. When society must choose, it must take into account the future as if it were the present. When an individual must decide, the present weighs heavier in the scale than the future. The individual has a right to claim, Who knows what the future will bring? It's not my responsibility. Indeed, in the case of two people walking in the desert, the great Rabbi Akiva rules that if there is only a canteen of water for one, let him drink and live; his friend must die, lest both die. Akiva's colleague, Ben Ptura, disagrees, saying both should drink and both should die. The commentaries point out that Ben Ptura wasn't wild. Why should both people die when one person can live? But his logic was, Let them both drink, for who knows what tomorrow will bring—tomorrow they may find water, someone will find them in the desert. If there were no possibility of finding water, then Ben Ptura would have to agree that the individual who has the water should drink it and should bid his friend farewell.

Of special concern in this whole analysis is the domino theory, also known as the slippery slope of medical ethics. Unfortunately, societal decisions can sometimes lead to amorality. Dr. Leo Alexander (1), writing after his return from the Nuremberg trials, commented on how was it that German medicine became the basis of immorality. How could it have degraded the human organism as never before? It was a time of triage, there wasn't money for everybody. That is how it started. Germany was in financial stress. The first medical decision was not to treat the incurables. That decision, Alexander says, ended up as: Don't treat anybody who disagrees with me. The next decision was; Kill everybody who disagrees with me.

Remember what happened to German medicine as a warning. Society may make decisions that seem to be necessary as triage, but concern for the future means concern that has an ethical basis. One of the Shattuck lectures (2) provides important data which the author unfortunately does not emphasize. The data reveals, as expected, that medical care improves for all with rising national income. However, Sri Lanka, the state of Coral in India, and the People's Republic of China have attained a life expectancy close to the level of the industrialized world—yet individual income levels are in the range of the least-developed countries. Only 16% of these improvements in health status of individuals can be attributed to rising income. Where does the other 84% come from?

Those improvements come from the heart and mind of those who decide triage allocations. To have to decide between an ICU bed and a new dialysis machine is one ethical level of a societal problem. But is it fair to choose between an ICU bed and mowing the parkway? Is it fair that our federal government publishes, at a cost of $100 million, nonsense literature that is never mailed from the government printing office, that is never even put into a stack for recycling? Who makes those decisions?

The improvements in life expectancy in China and India—84% of those improvements—come from believing that every individual in the country must have good medical care. It is possible to make ethically beneficial triage decisions even with severely limited income. Societal decisions must not be made from an amoral perspective that exempts society from ethical imperatives, but rather with a full appreciation of the infinite worth of human beings that will enable us to do a lot more with the little that we have.

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Triage: From Departments to Patients

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In the relationship between the department and the patient, can the department be completely independent? In a 1976 conference entitled "The Moral, Ethical, and Legal Issues Facing Medicine" that addressed the delivery of extraordinary care, it was noted that those of us involved in the care of patients with renal failure had an opportunity to evaluate the ethical, moral, and legal problems facing the delivery of such care. We had a unique opportunity to discuss the issues and possibly come up with some answers before national economics determine allocations for us. We lost that opportunity. Now we have made a complete cycle and are now discussing this issue again.

Dialysis as a Model

The best model for the discussion of the ethics of the allocation of scarce medical funds and resources is the funding of dialysis care in all its vicissitudes.

The national end-stage renal disease program mandated by act of Congress in 1973 ensured equal accessibility and equal quality of care to all Americans who needed either an artificial kidney or a kidney transplantation. That was in 1973.

From 1968 to 1973: Scarcity. In 1968, in a presidential address to the American Society of Nephrology, Dr. Neil Bricker, director of the Department of Medicine of Washington University, questioned whether delivery of this kind of care in his own department and elsewhere to a few thousand patients needing artificial kidneys to live would divert economic resources away from other possibly more productive healthcare activities such as basic research, teaching, and primary care. At that time, about 2,000 persons needed this type of care each year, at a total cost estimated as rising to about $1 billion after two decades. Dr. Bricker's feeling was that the care given to these patients would interfere with departmental research and teaching programs. Between 1968 and 1973, the U.S. government spent no more than $8 million on kidney research per year. Therefore, the money was never allocated in either direction.

During those years, the ethics of the allocation of funds and resources to such kidney patients revolved around two questions. First, decisions on who should live and who should die had to be made according to policies from government, third-party payers, hospital administration, and departmental directors. Second, departmental directors and specialists within their departments had to resolve conflicts over whether care of such patients would benefit the department itself or its growth. Departmental growth was seen variously as depending on basic or clinical research, or on research of any kind, rather than on care by dialysis. In other words, the problem was a conflict of interests within the department itself, not the ethical dimensions of giving renal care.

On the other hand, a small group of patients had renal failure. They wished to live and fought hard from below with all the authorities to make these resources available to themselves, the few that needed it. What is most important about this situation is that triage was being performed both knowingly and unknowingly. Most potential dialysis candidates did not know what care was available to them and therefore did not get near a system which could provide it.

Many departments were faced only with taking care of a few patients with limited departmental resources; these departments considered the problem to be limited. The amazing misconcep-

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tion was that only a few thousand persons in the entire country needed but were not able to receive treatment. Actually, triage had already taken place through lack of knowledge of the incidence of need, lack of knowledge of the viability of the treatment, and lack of knowledge by patients of the potential medical resources. Therefore, the artificial kidney was considered to be extraordinary care for any patient and unreasonable for most, though it might be usable for some few. Decisions were not made directly either by a committee within a department, by ethicists consulting a departmental chairman, by moralists, or by religious leaders. Basically, decisions were based on the needs of the particular hospital, and more particularly on the needs of the department; not least, decisions were influenced by specialists in the field.

From 1973 to 1981: Unlimited Funds. This model changed in 1973 when amendment 92603, specifying that all artificial kidneys and transplantation would be paid for by Medicare, was added to the Social Security act. By law these therapies had to be equally accessible to all Americans, and quality of care had to be monitored. That law resolved all ethical and moral problems for everyone.

We then learned that the number of persons who actually needed an artificial kidney, that is, dialysis, wasn't 2,000, or 20,000—it was 72,000. Where did they all come from?

The law removed any need to debate the use of dialysis because the funds seemed infinite. The care which had been classed as extraordinary and nonusable suddenly became ordinary care. Patients with multiple medical problems who would previously have seemed unreasonable candidates for dialysis—the aged, the hard to rehabilitate—became reasonable candidates for such care.

Have there been recent meetings about the ethical and moral implications of using Medicare funds to maintain people on artificial kidneys throughout the United States? No. The cost per patient has not risen in eight years. Actually, it has decreased, because the total number of patients being cared for has tripled. However, the total cost of the program has become a problem to government.

From 1981: Scarcity. At the present time [November 1981] the government is making the decision to cut the total cost of the program across the board, again bringing us all back full cycle to another discussion of what we should do now when infinite resources once again become finite. So where does this bring us? This brings us back to the department and its relationship with its patients.

During the eight-year heyday of unlimited Medicare dollars, the departments were able to expand their programs because they were funded. Many hospitals organized renal programs and built renal centers because it was profitable. The income enabled them to support other programs within their department. No triage decision was ever made to exclude a patient.

With the current change to limited funds, do the department members or the director sit down with a nonmedical group of people representing our society to discuss the decreased allocation of funds or the decreased resources to the patients that the department is required to take care of? Not at all. The department is influenced first by what government resources will be available; second, by what the board of trustees would like the hospital and the department to be; third, by what the hospital administration's relationship is with that department; fourth, by what the departmental director's relationship is to the faculty and members of other medical disciplines.

Judgments on allocation of funds and resources to specific disease entities and age categories are based on such factors as the cultural backgrounds of the decision-makers and the religious beliefs of the different influence groups. But in most cases, the judgment is decided by the political choices and the power of individual physicians advocating either for their programs or for their patients. In these instances, the medical moral codes set forth in the oath of Hippocrates and later in the Declaration of Geneva, the Nuremberg code, and the Declaration of Helsinki are inextricably entangled with the power politics, the influence, the desires, and the goals of individual physicians and departments. It has been presumed that physicians' adherence to the traditional principles would be best for all patients. However, Pellegrino pointed out that questions of life and death, the choice of medical intervention, and the duties of physicians to deliver different aspects of medical care were left entirely to physicians themselves and then to those above them, the director of their department.

The department's choice to deliver sophisticated care to a group of persons—whether small newborns less than 800 gm or the aged who are in renal failure—is directly dependent on decisions made within the department itself and—less often—outside the department. These decisions can be influenced by a patient's demand upon a physician, who may be able to obtain the resource from his department through personal influence and reputation. Or patient groups may influence the government and third-party payers to begin supporting a mode of therapy which then becomes profitable for the department to develop.

If There's No Resource, Need for the Resource Decreases

Although ethical and moral considerations are said to be considered, in reality none are. We are now in an era of reduced resources and every day we in medicine face the allocation of funds for programs. How will triage work in this atmosphere? I predict it will start at the level of the physician caring for the patient. If no resources are available, the patient will not enter the medical system. Sooner or later the patient will disappear from the list of those needing a particular kind of care and the patient will no longer be considered triaged because the program doesn't exist. Since that resource will not be available, the patient cannot receive it. Since one patient cannot receive it, future patients will not seek it; and if a patient does not seek it, that patient is simply not triaged any longer.

In the early days of dialysis, patients with high blood pressure and diabetes were not considered as candidates. Since they were not considered for dialysis, they never showed up in any statistic registering need for dialysis. It became a medical fact that dialysis care for these groups was extraordinary, unusable, unreasonable, and out of the question. With the advent of equal accessibility to care, the "medical fact" was changed completely.

In summary, within the department of a hospital, allocation of funds and resources to patients will be made not by overt decisions after discussions, but by indirect methods, such as what is the government funding now? What is the department's most important need? What does the department need to become outstanding? Certainly decisions will not be made through realistic evaluation of moral and ethical problems. Triage will take place subconsciously; neither the department, the physicians, nor the patients will realize it has taken place. The historical truth is that if there's no resource, the need for the resource decreases. This truth will solve some of the moral and ethical problems we face.

One of my Russian colleagues told me, "Everybody in Russia can get dialysis." I asked, "How many dialysis machines do you have in Moscow?" "Four," he answered. In other words, since the availability of machines in Moscow is limited, the number of patients sent to Moscow to use the machines is limited. Those who survive to get there are dialyzed. That is finite resolution of the allocation of limited resources and funds. There are no rules. There is no structure. There is no way to evaluate what a department decides to do. Basically, the decisions depend on what is best for the department and the individuals at that time.

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Rabbinic Comment: Triage of Resources to Patients

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The word "triage" has its origins not in medicine but in agriculture, where it was used to describe the process of culling coffee beans into the broken, the semibroken, and the whole in order to determine which to save and which to cast aside. How little things have changed. Still, although the original use of the term was premised upon agricultural abundance, its use in modern medical practice, stemming from the experience of treating battlefield casualties, is based upon scarcity. Now, "triage" is the single word expressing the great moral dilemma of who to save when not all can be saved. Before examining the traditional Jewish attitude toward the allocation of scarce medical resources, I must first tender some preliminary observations about the general ethical problems raised by the question of triage and the allocation of scarce medical resources.

First, the determination of what constitutes a scarce medical resource is societally relative. A scarce medical resource at The Mount Sinai Medical Center might be a CAT scanner or a dialysis machine, while in the hills of West Virginia a scarce medical resource might be a simple dose of penicillin. People imagine, often quite incorrectly, that the problem of triage is occasioned solely by the stunning breakthroughs in medical technology that are either too expensive or too rare to be available to all in need. In fact, the misallocation of common and existing medical resources often creates the situation of scarcity. In such a case, I strongly believe, the philosophers of medicine do a great disservice by attempting to present morally acceptable models for the allocation of unnaturally and unfairly scarce medical resources of the land.

Though a society may not be obligated to provide the state of the art in medical science to every village and hamlet, the basic medical needs of the population must be assuredly met. Any discussion of triage that does not first address the gross distortions of the present system in providing medical care has too easily accepted false scarcity as a given fact, making the discussion of triage both premature and unfair.

With this important social caveat in mind, the genuine existence of scarce medical resources for reasons that are more or less defensible is a fact of current medical practice, and the vexing philosophic issues raised by real scarcity must be addressed by philosophers and theologians, since they are being addressed by default in the medical wards of every hospital and clinic in the country every day.

Moral Issues in Triage

The first of the important philosophic issues raised by triage is the question of whether withholding or withdrawing medical treatment from one patient in order to provide it to another is ever morally justifiable. James Childress calls this the "criteria of inclusion" (1). By this he means the way in which the medical acceptability of a potential patient is evaluated. In the language of triage, this is the question of the "first cut," the evaluation which determines that some potential patients ought not to be treated for certain reasons. This determination that some are worthy and others are not depends, I believe, on a clear understanding of the implicit operative concept that I shall call "therapeutic hope." By this I mean the concept that the medical procedure contemplated for a potential patient (or the medical procedure whose continuation is in question for an existing patient) holds out the realistic possibility of either curing or postponing, for an extended period of time, the life-threatening consequences of the patient's condition. I shall set aside for the moment the vexing question of whether palliative care—the alleviation of pain—is therapy.

The second moral issue of triage, again follow-

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ing Childress and Nicholas Rescher (2), is the "criteria of selection." These criteria pose the question of whether good reasons exist for further excluding some patients who have met the test of medical acceptability posed by the "first cut" but would now be excluded because their degree of therapeutic hope is not as great as others in the group of medically acceptable potential patients. Simply put, among the worthy there are those who are more worthy.

The Jewish View

On the issue of the first evaluation in triage—the question of refusing medical procedures to those without therapeutic hope—I believe a careful and accurate reading of the sources confirms that Judaism approves of such a withdrawal or withholding of medical resources. The Jewish issue turns on the implications of the command in Exodus 21:19, *rapo yirapeh,* which is interpreted by Jewish sages as the warranting passage for the medical arts. The physician is allowed, even commanded, to heal. But what is the nature of his or her *chiyuv* (obligation) when therapy is no longer possible? At such a time the physician is, as it were, not a physician, not even a potential provider of treatment which can change or alter substantially the course of the illness, and must *shev v'lo ta'aseh* (stand and do nothing)—not because there is something to do and he or she is too craven or frightened or unkind to do it, but because there is simply nothing more that the medical arts have prepared the physician to do.

The rabbinic tradition knows of people for whom there is no therapeutic hope; the state of being near death is called *gessisah,* and the person in extremis is a *gossess.* The Code of Laws rules, for example, that a woodchopper working outside the window of a *gossess* and making enough noise and clatter to keep the *gossess* alive may be removed so that death may be allowed to take its natural course. I have not been charged with discussing the related but different issue of euthanasia, so I shall not proceed further with a discussion of limiting care for the dying. Suffice it to say that the Jewish legal tradition, though obviously unchallenged until lately by the profusion of medical technologies to extend life, was well aware that, at some point, a patient is no longer a patient and a doctor no longer a doctor with regard to the commandments to heal and be healed.

If a philosophy of triage recognizes only the *gossess* as being beyond therapeutic hope, the refusal to treat would, in my opinion, be acceptable in the Jewish tradition. Furthermore, this would be true even if the medical resources required to treat the patient were not scarce. The warrant for the first cut is thus not scarcity, but the absence of therapeutic hope.

The truly vexing and vicious moral dilemma of triage thus does not emerge until the second cut is faced, and here Judaism has a very strict and clear view, stated in the famous talmudic maxims, "What makes you think your blood is redder than the blood of your neighbor?" (*mai chazita*) and "We do not set one life over and against another life" (*ain dochin nefesh mipnei nefesh*). The overriding and equal sanctity of all human life makes Judaism unable and incapable and unwilling to differentiate between the worthiness of one life over a neighbor's.

To be precise, there are occasions recorded in rabbinic law which do involve setting one life against another, but upon inspection all of these cases turn out to lack relevance to the case of triage. First, various sources indicate that in a case in which the welfare of an entire community is at stake, an individual may be sacrificed only if the person is already guilty of a capital crime (*chayev mitah,* "deserving of the death penalty")—but this is clearly irrelevant to the situation of an innocent person in need of scarce medical resources.

Secondly, the Sifre (commentary) to Leviticus 25:36 and the Babylonian Talmud, tractate Baba Metzia 62a, record an account of two men in a desert with only enough water for one. If both drink, both will die. If one drinks, he will be able to reach the oasis. In this remarkable precursor to the famous triage case in nineteenth-century American jurisprudence, *Holmes* v. *United States,* we seem to have found a case of true relevance. The ruling in this case is that the person who owned the canteen of water ought to drink and save his own life at the expense of his companion. Rabbi Akiva ruled: *chayecha kodmin l'chayeh chaverechah,* "Your life takes precedence over the life of your friend." However, in this case, several later rabbinic exegeses indicate that the critical factor in Akiva's ruling was that one of the men owned the canteen and was thus in a position of saving his companion only at the cost of killing himself, something which the rabbinic value—that your blood is no redder than your neighbor's—prohibits. If the canteen were found or owned jointly, the ruling would be different. In any event none of the people in need of scarce medical resources owns those resources and thus none can act to use them on the basis of the desert analogy in Baba Metzia.

Finally, there does exist a truly discordant treatise which seems to support a type of hierarchical scheme in which some persons in a situation in which not all can be saved are to be preferred over others. In the Babylonian Talmud, Mishnah Horayot 3:6,7, we learn that a man must be saved before a woman, a cohen before a levite, a levite before an Israelite, an Israelite before a mamzer, etc. No discussion of the reasons behind this incredible ruling are given, but we may surmise that those who are more liable for *mitzvot* (good or meritorious deeds) are to be saved first. Still, this all flies in the face of both "do not set one life against another" (*ain dochin*) and "your blood is no redder . . ." (*mai chazita*).

The philosophic literature is full of hierarchical schemes for triage in which such diverse factors as social worth, family status, and life expectancy are all proposed as relevant criteria for the selection of those to be treated with scarce medical resources. Nonetheless, Judaism resists such hierarchical schemes and the mishnah (codification of oral law) in Horayot stands alone in its affirmation of such a view.

To further indicate that Judaism has never regarded Mishnah Horayot as definitive in life-and-death situations, we have only to examine the rabbinic rulings during the Holocaust to see in their poignant affirmations of the sanctity of life the true normative Jewish teaching on the equal value of all life. Rabbis like Mordecai Yaakov Breish, Shimon Efrati, Ephraim Oshry, and Zvi Hersh Meisels have all left records of the most horrid questions, and their thoughtful responses must leave us all in awe.

One example: Rabbi Meisels writes of a selection in Auschwitz on the eve of Rosh Hashanah (new year) 1944 in which 1,400 little boys were to be chosen to be killed the next day. Parents were rushing around trying to redeem their sons from the Kapos and some came to Rabbi Meisels, a prisoner in Auschwitz at the time, to ask him whether it was possible to redeem a boy knowing that his redemption would be at the expense of another to be taken in his stead. Using the foundations of *ain dochin* and *mai chazita*, Rabbi Meisels refused to rule on the question. This was taken, quite properly, as a negative ruling, and the person did not redeem his son.

In another case of the same type in which the person to be redeemed was a bright talmudic scholar, Rabbi Meisels also ruled negatively, citing Rashi to Yoma 82b and the commentaries on Baba Metzia 62a by the Maran Hareem, who told the story of Moshele the water-drawer who lived in a city with a great rabbi; when asked who should be sacrificed, Moshele or the rabbi, if a crowd came and demanded one of them, the Maran Hareem answered that both were of equal value in the eyes of God.

In our own time the great rabbinic authority Rabbi Moses Feinstein was asked to rule on a situation in a hospital in Israel which had limited doses of penicillin and several patients on the ward who needed it. He ruled that the proper Jewish course of action was to give the penicillin to the first person the doctors encountered who needed it.

It is my contention that if the rabbis ruling in the depths of the kingdom of night and the rabbis ruling in the battlefields of Israel are consistent maintainers of the values of *ain dochin* and *mai chazita*, which affirm the equal and supreme sanctity of life, then we must rule so as well in our less severe circumstances. We cannot, as Jews or in morality, sanction setting one life against another. The allocation of scarce medical resources must thus be done by fair and totally arbitrary and random selection among all those who possess therapeutic hope. Only in this way can we preserve our moral and spiritual fiber while struggling for a day when medical scarcity will not plague us, or our children, or the children of our children.

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Triage of Scarce Resources: Discussion

Moderator: Donald Gribetz, M.D. Discussants: Martin S. Begun, Thomas C. Chalmers, M.D., Rabbi Marc A. Gellman, Ph.D., Ira Greifer, M.D., and Rabbi Moshe D. Tendler, Ph.D.

Questions were posed by members of the audience and were read by the moderator.

Question: The last speaker mentioned that triage is in principle evil. Rabbi Tendler mentions that, as far as Jewish law is concerned, a different ethical basis is applied to society than that applied to the individual. Could you please elaborate?

Gellman: The basic premise, as far as Jewish law is concerned, is that triage at all levels—societal or individual—is evil. Jewish law dictates, when confronted with the ordering of giving aid to people, be it medical or financial, that the question is who gets help first. It is never a decision between someone getting help and someone else being left out. The classic example of two people in the desert—if they share the water and live today, they chance what is going to happen tomorrow—applies not only to individuals but to society as well. It is very rare in Jewish practice that any community would say we're going to help one group of individuals and leave others out.

Social Management of Smoking

Question: Dr. Chalmers raised an interesting point about the sociologic and economic problems that are created by the bad habits of luxury in our society. It is true that the surgeon general has recognized that smoking may be harmful to your health. But government has not chosen to do anything about it. There are precedents in history in which government recognized that people indulge in habits of luxury which, on the whole, were detrimental to the health of society. Therefore, government should recognize that individuals may choose to indulge in habits which the government cannot legislate against, as was tried in prohibition. At least the government can ask people to bear the cost of the extra medical expense. That would be a way of paying back society for the individual's bad habits of luxury. If you choose the habit, why not pay for it? Precedents have been set for heavily taxing tobacco and heavily taxing alcohol or gambling. If government can recognize that people will do these things and that it is not ethical to legislate against them, at least have the people pay part of the expense of the extra cost to society which is generated by these bad habits.

Tendler: The point raised is intriguing, as is the whole issue of triage. Triage began, as Dr. Chalmers correctly said, with a chronic lack of funds. Can an individual direct triage decisions because he or she can afford it when others cannot? In a triage situation, could you argue for another incubator to be added to the neonate unit because your community can afford to direct funds to that need? It's your money, you can do what you want with it. When you extend this to a societal level, what you are essentially saying is, Could the rich of society demand that the concerns of society be directed to their interests? You may say, tax tobacco so that the cost of lung surgery or emphysema is covered by the people who smoke. It is a valid point, but, nevertheless, is it ethical to allow such a thing to happen? Essentially, what we're saying is that society will now accept the decision of smokers. They want to get lung cancer and society will minister to their needs because they will pay society to set up more clinics and more pulmonary surgery units. Does society not have an obligation to avoid the ethical decisions of the individual? Can society say, you're not going to get operated on if you get lung cancer? The surgeon general has issued an ethical ruling that smoking is dangerous to your health. Yet Congress votes increased support to the tobacco lobbies. This is where the ethical issue of triage comes in. I would be very upset about individuals directing social concerns, let alone allocation of funds, for what is basically a decision of society. This is unethical behavior.

Chalmers: There may be a more ethical solution to the smoking disease problem. Twenty years ago, if you went to a medical meeting, 90% of the doctors smoked over a pack a day. If you go to a medical meeting now, it's probably around 5%. That is not because doctors are necessarily more intelligent than the 50% of the adults who continue to smoke. Doctors are just better educated. They have been taught about what happens to you if you smoke too much. They have quit smoking. Therein lies the solution to the smoking problem. The trouble with raising taxes is that it just creates bootlegging. What we should be doing, with the tax or with other federal funds, is a more intensive antismoking campaign.

Money Sources and Research Results

Greifer: Both Dr. Tendler and Dr. Chalmers quoted from Leo Alexander. It is of interest to me that your subject was ethics in governmental institutions. The paper in *The New England Journal of Medicine* cited in respect to rehabilitation of patients on dialysis commented that basically half the patients were not rehabilitated, and that since they were not rehabilitated, why keep them alive in the first place? I am upset about the ethics of an institution accepting money to do such a study when, in fact, it knows what the outcome would be. In a sense, ethics would be used by those forces which might want to reduce or set a standard or set the social conscience against it. The first step in the progression Leo Alexander described has certainly taken effect in this country already. Is it ethical for the government to do this? Is it ethical for an institution to accept funds to do this knowing in advance that maybe they know the outcome? Should we kill off patients with arthritis because they can't go back to work? They're costing the government a lot of money to keep them alive. Is this logical?

Question: Martin Begun and Rabbi Tendler said something about problems with rich people directing things. You spoke at great length about industry and academic institutions. But what about rich people who have foundations, such as the Rockefeller Foundation and the Ford Foundation? How does an institution sort out ethically and how do foundations behave ethically?

Begun: Foundations, as a matter of record, are similar to government. There are fewer strings on foundation gifts for basic research than one would suppose. It's the private philanthropist, the corporation, which we're going to have to contend with more and more as the corporate world begins to see certain economic benefits from academic and basic science activity. It is the corporation that is going to contractually demand a greater voice in how a physician conducts basic research and how that research is marketed. In my experience, foundations are just like the National Institutes of Health. There may be one or two exceptions to that rule but with the more reknowned foundations, the person accepting a grant knows exactly what the framework for utilization of that money is. There are no hidden surprises. Both the protocol and what the terms of acceptance are, are known. You can operate in a free-wheeling academic environment with research funds from a foundation as well as from any governmentally sponsored research program.

Question: Dr. Chalmers, how are we going to handle the growing number of foreign governments giving money to academic institutions?

Chalmers: The impoverished institution is going to face a lot of ethical dilemmas in the next few years. Foreign money is really no different from American money. It is money that is the root of the evil that we are talking about. People don't usually give money unless they want something in return, with the exception of some foundations and the federal government. Industry doesn't really give money unless there is some string attached. We must build many barriers to protect the sciences.

For example, there are two methods by which pharmaceutical firms have blundered clinical trials in the last few years. One company gave $5 million to a nonprofit foundation on the condition that a clinical trial of the company's drug be set up. The contract called for the appointment of a policy board that would make decisions about the protocol, about whether to undertake the study, how to conduct it, and when to conclude it. The conclusions drawn were to be totally independent of the pharmaceutical house. The company, as part of the contract, agreed they would not use any of the results of the study for advertising purposes unless the results were published, and agreed that the decision to publish would be entirely up to the policy board. This is a way in which industry money can be used for the good of the company.

In contrast is another study in which the group running the study was beholden to the pharmaceutical firm throughout. The data were analyzed by the pharmaceutical firm. The paper was written by the pharmaceutical firm and published with the support of the policy advisory board—supposedly independent people. After the study was published, the Food and Drug Administration refused to approve the drug because irregularities in interpretation of the data had been so blatant that there was no reason at all to advocate use of the drug. Yet the conclusion of the study was that the drug is highly useful and should be used right away.

These two cases are quite different and not necessarily venal in their outcome. The second pharmaceutical firm did not recognize the importance of bias in the interpretation of data. People who made their living in the firm looked at the data and concluded it was a great drug. Outside neutral groups analyzing the data concluded that the drug was not a great drug at all. This is what I mean by unconscious bias. The only way to control it is to put definite barriers between the source of the funding and the results.

Undoubtedly there are rare instances of people doing NIH-supported research fudging their data to get positive results. Some do it consciously. But I suspect most do it unconsciously because of the researcher's overwhelming need to get certain results in order to make a living. The problem exists with federal or foundation funding. It is much worse in the direct hands of the industry that is involved. That's why there is all the fuss about Massachusetts General Hospital's use of the $50 million from a pharmaceutical company. I think the fuss would be there whether it was an American company or a German one.

Reaching Institutions

Question: Without education, we're not only going to fudge results, but fudge the whole ability to function properly in our society. What method could be used to begin to educate institutions? Government is beyond, beneath, or above education. You can't educate our president any more. It's not going to do him any good.

Chalmers: A project studying massive doses of steroids for treating aseptic shock in intensive care units was refused by the funding agency. The agency was impressed with the protocol, but there's no money for the proposal. The time just doesn't seem right to get money for such a grant. I asked the proposal author, "What's going on now? Are people using massive doses of steroids for septic shock?" He said, "There are two schools of thought. Some use it and some don't." I said, "What will a doctor do? You're now in a position to train younger physicians. What will you tell your residents to do when they have a case of septic shock?" He said, "I don't know yet. I'm waiting for my results to come in from my study but I can't fund the study. I don't known what to do." No one objects to paying for the steroids or for the care for these patients in intensive care units, one of the most expensive areas in hospitals. Yet nobody, including third-party payers such as Blue Cross, Blue Shield, and insurance companies, has a way to reach institutions. You could say how much money would be saved if the study were funded and how much treatment would be better. Some patients would not be treated with steroids, others would be. The result is that limited resources would get better mileage. Yet we don't seem to have an open channel of communication. We can talk to medical students and maybe even to government. Somehow, there is no way for the individual who has a point of view to speak to institutions, unless he happens to head that institution. This is a frustrating breakdown of communications, which must somehow be opened up again.

The ethical values of an institution are those of the people who run it. The institution has no ethics and no morals other than that of its people. For this case there is a simple solution. A relatively easy study can be done. You might give or you might not give the steroids. You can record the results without any extra costs, whether the patient lives or dies. You don't know which one has the better chance of living or dying, so the study can be done at no cost. Because the third-party payers will pay for steroidal treatment at the moment, although perhaps not in the future, the research is just a matter of the doctor working a little harder to go around more often, to be on call night and day, to come in when the patient is in septic shock. Since reality, not theory, is what determines ethics, you have to be up all night. But surely institutions would save a good deal of money in one year by getting the results of a study.

Greifer: A few years ago, a paper described the ethics of triage and the ethics of constant medical practice. Can we deliver everything that we have in our heads? The answer is no, for several reasons. Not only have we changed, but also the institutions in which we live have changed. Years ago, young doctors worked every other night or two out of three nights. Today, they work every fourth night. There are a lot of differences.

One discussion called for two kinds of money—green money, which is hard dollars that work on a basis of getting things done that we really need, and blue money, essentially service money, not only for doctors but for the society within the institution, meaning service above and beyond what is necessary now. If a man wants your care as a physician can he only use so much green money to get it? Mowing the lawn becomes important to him. If he mows your lawn, he earns a certain amount of blue money. The question of green and blue money addresses the issue of services that can no longer be paid for with hard money. We have neglected this in our own institutions. Years ago it was common for house officers to write papers and to make observations. There is very little of that done today. It was not uncommon for a volunteer physician to collaborate on projects. That is seldom done today.

Budgeting for Future Needs

Question: Rabbi Tendler, is a hospital permitted to base expenditure on caseload? Is it obligated to exhaust all available funds on all present patients? Does the hospital take into account that next week there will be X number of patients requiring treatment? The entire monthly budget may be at my disposal now. Does the hospital use that budget in the first week that patients present themselves, or does the hospital have a choice in expenditure?

Tendler: The question is theoretically valid. Given that ten people will die tomorrow for the want of treatment, should I let five die because I fear that tomorrow five, or ten, more patients will come? Obviously in a real situation, you have to treat the patients that are ready to die now. You can save them. You can't say, I'll let you die for someone else. I think your question has real merit when you are speaking about the funding of hospital programs. A community health education program can give tremendous benefit in ten years if we stop smoking instantly today. We most likely would have enough money to fund all our medical needs. Should we spend money for poking away at that problem, educating the populace? Should we spend it all for building more intensive-care beds, more pediatric units with nobody waiting at the moment or dying from lack of care?

I have two future concerns; one is the immediate future and one is the future future. This is where the ethics and morals of the institution, or the individuals who run the the institution, come into play. The needs of society can justify a future future for you without neglecting the immediate future. But no ethical system will allow you to neglect the immediate needs of a patient waiting now for your care.

Triage of Patients

Greifer: Most discussions of triage involve the principle first come, first served, based on which patients have been thought qualified for care based on medical knowledge. My question is, Is that medical knowledge in any way influenced? The first cut is not based on whether an individual can qualify for care based on medical knowledge itself, but is influenced a great deal by the availability of resources. You may say all qualified people will be cared for, but who makes that list?

Tendler: As Dr. Gellman correctly pointed out, the tradition of Judaism indeed does not allow for selection of patients on the basis of so-called respective worth. Yet he cited this very complex and difficult example.

Major ethical-moral distinctions may be needed between an individual being asked to make a decision and society being asked to make a decision. Societal factors may have entirely different axioms to go by. I suggest that the discussion in the Talmud of selection of people is never on a one-to-one basis, but, rather, when society must make its decisions. These are triage decisions. The issue at hand is, does society have a right to preserve values as a society? Do the same factors which come into play—not choosing one individual life over another individual—apply? Does this apply to legislation, to departments, to institutions? This is our topic.

My father-in-law, Rabbi Feinstein, was asked for an opinion in a strange case of triage. Now it is not considered strange but then it was the first such case. Penicillin had just arrived in Israel. There were eight meningitis cases at Hadassah Hospital. Rabbi Herzog didn't want to take responsibility on himself to rule on this case, so he called Rabbi Feinstein in New York and asked him to join in a discussion of what should be done with the one patient cure dose that was available. There was enough for 11 injections. Who should receive it? Without a 30-second hesitation, Rabbi Feinstein answered, "The first bed you come to."

Question: What do you mean by therapeutic hope? Can a doctor really make a legitimate decision to withdraw care? If someone has terminal cancer, is the doctor, according to Jewish tradition, permitted to stop treatment—I mean painkillers or supportive treatment? What if the patient asks for it?

Gellman: The answer to the last question is no. The reason is that I didn't specify the exact dimensions of what I mean by therapeutic hope because it takes us into the area of euthanasia. It does require further definition. There are two definitions for therapeutic hope, a lenient and a strict tradition. The lenient tradition says that as long as there is no possibility of cure, of reversing the condition, that the person is actually devoid of therapeutic hope and any medical procedure to be conducted would be classified as experimental or, if not experimental certainly not of therapeutic value. I would not endorse such a liberal tradition, though neither would I say that no case could be made for it.

The more conservative position on therapeutic hope would require that the person actually have entered the death process. Again, the traditional definition of death is when death is expected within 72 hours or so—an almost immediate situation, really a virtually certain diagnosis. As long as any possibility of extending life for any amount of time, through any treatment, exists, the doctor is still under obligation to heal. Such acts, even though they cannot reverse the condition, would simply extend life. These acts would be obligatory on the doctor. The doctor is required to treat. I would endorse this position.

Medical Ethics as a Discipline

Gribetz: There is a dilemma now of establishing ethics as a discipline. There are many institutions around the world that have what are known as ethics rounds. They make rounds at the bedside and discuss the very question that you raised, plus others. It is believed now by many of us in medicine that ethics rounds should include the doctor, the parents if it's a child, or the relatives, the nurses, the medical students, the house officers, the social workers, sometimes the lawyer of the hospital (for obvious reasons), and the ethicists—the rabbi or priest. There are very difficult decisions to make because many factors enter into a decision. The contention of the ethicists is that if you bring these problems into the open, even in individual cases, consensus develops from such a discussion.

What we're all saying is society is deciding. Society is the group of people who are around the bedside of the particular patient. This is beginning to happen more and more. No longer can a doctor go to a bedside by himself and turn off a machine or withhold treatment or make some other decision. We're way past that. Society now demands that it take part in the decision.

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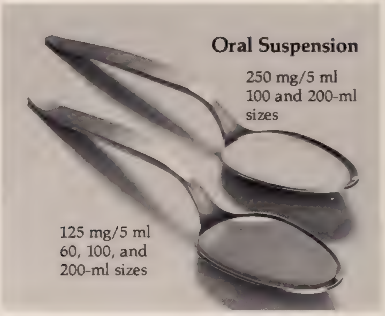

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Volume 51
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April 1984

CONTENTS

Introduction *David A. Dreiling, M.D.* 121

CEDARS-SINAI MEDICAL CENTER

History and Introduction 123

Fibromyalgia: Unusual Historical Aspects and New Pathogenic Insights *Daniel J. Wallace, M.D.* 124

Parathyroid Hormone Measurements in Hemodialysis Patients as Assessments of Renal Osteodystrophy *Wade M. Aubry, M.D., James C. Sparks, Ph.D., and Glenn D. Braunstein, M.D.* 132

Elastofibroma Dorsi *Myles Edwin Lee, M.D., Delver R. Cain, M.D., and Carlos Blanche, M.D.* 138

Laboratory Testing on Admission to a Teaching Service: Expectations and Outcomes for Serum Electrolytes *Glen H. Murata, M.D., Edwin Muranaka, M.D., and A. Gray Ellrodt, M.D.* 141

MOUNT SINAI HOSPITAL MEDICAL CENTER OF CHICAGO

History and Introduction 149

A History of Medical Research at Mount Sinai Hospital Medical Center of Chicago *Maxwell P. Westerman, M.D., and Stan Tymorek, B.A.* 150

The Practice of Tubal Sterilization: Review of a Departmental Practice Pattern *Norbert Gleicher, M.D., Gunter Deppe, M.D., and Jan Friberg, M.D., Ph.D.* 157

A Hospital's Response to the Increasing Incidence of Child Abuse and Neglect in an Inner-City Population *Howard B. Levy, M.D., and Stephen H. Sheldon, D.O.* 161

Effect of Splenectomy on the Growth of Carcinogen-Induced Experimental Bladder Cancer in Mice and Rats *Eugene P. Ornellas, Ph.D., Ann O'Brien, M.B., William Thomas, Jr., M.D., Robert E. Lee, M.D., Richard C. Moon, Ph.D., and Maxwell P. Westerman, M.D.* 166

continued

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CONTENTS *continued*

Effects of Cryopreservation on Lymphocytes of Homosexual Men with Generalized Lymphadenopathy *M. Venkataraman, B.V.Sc., M.Sc., Ph.D., and Maxwell P. Westerman, M.D.* 174

Iron Absorption and Utilization in Maintenance Hemodialysis Patients: Oral and Intravenous Routes *Lilliam Magana, M.D., Sisar K. Dhar, M.D., Earl C. Smith, M.D., and Charles Martinez, M.D.* 180

Stereologic Analysis of Muscle Capillaries in Selective Atrophy of Type 2 Myofibers *Marcelino G. Reyes, M.D., and Edward S. Yastrow, B.S.* 184

Renal Dysplasia and Chondrodysplasia in the ch Hydrocephalic Mouse: A Cellular Model of Defective Differentiation and Organization *Robert R. Richardson, M.D., and Marcelino G. Reyes, M.D.* 188

Changes in Free Histamine in Peripheral Circulation following Cockroach Antigen Challenge in Asthmatics *J. L. Chang, M.D., U. Yun Ryo, M.D., and Bann Kang, M.D.* 197

Reproducibility of the Red-Cell Adherence Test: Technical and Practical Considerations *Jaroslava Mlsna, B.S., Albert I. Rubenstone, M.D., Marcelino G. Reyes, M.D., William Thomas, Jr., M.D., and Rita Noronha, M.D.* 203

Propranolol-Induced Myotonia *L. Jay Turkewitz, M.D., Vinod Sahgal, M.D., and Alfred Spiro, M.D.* 207

MOUNT SINAI MEDICAL CENTER OF GREATER MIAMI

History and Introduction 209

Iatrogenic Disease: An Overview *Federico R. Justiniani, M.D.* 210

Effect of Inhaled Ipratropium Bromide on Tracheal Mucociliary Transport in Bronchial Asthma *Jack A. Bell, M.D., Barry M. Bluestein, M.D., Ignacio Danta, M.D., and Adam Wanner, M.D.* 215

Papillomas of Prostatic Urethra with Prostatic-Type Epithelium: Report of Eight Cases *Jack Lubin, M.D., Thomas M. Mark, M.D., and Amery R. Wirtshafter, M.D.* 218

Effects of Hydrocodone Bitartrate on Breathing Pattern of Patients with Chronic Obstructive Pulmonary Disease and Restrictive Lung Disease *Marvin A. Sackner, M.D.* 222

Index to Advertisers

Allied/Regency Medical Laboratories	cover 4
Eli Lilly and Company	cover 2

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Introduction

The *Journal* is pleased to publish here a special issue commemorating the affiliation with it, beginning in January this year, of three notable institutions—Cedars-Sinai Medical Center in Los Angeles, Mount Sinai Hospital Medical Center of Chicago, and Mount Sinai Medical Center of Greater Miami.

This issue introduces each of them in a brief history and description of the institution, and then in papers originating in the medical center.

For the last sixteen years the *Journal* has been the published voice not of one hospital, but of a large medical complex, including five hospitals, a medical school, a school of basic sciences, and several smaller centers of learning. Expansion of the *Journal* to encompass the three new institutions is particularly apt in this fiftieth anniversary year of the publication.

Like the Mount Sinai Medical Center in New York, each of the three is an urban tertiary health care center serving a diverse community.

The addition of the three new affiliates gives the *Journal* a wider plinth on which to rest. It raises our subscription list to 6,000. It makes a more varied source of material available to our readers and affords a wider base for our panel of reviewers. It makes distribution of the *Journal* truly national. It brings monthly publication—an aim of mine since I took on the editorship—well within the realm of future planning.

Above all, this new affiliation is in line with current policy:

First, continuing to encourage authors to submit high-quality papers for refereed publication.

Second, expanding our special sections (Radiologic Notes was the first of these) to include the major disciplines and specialties. These sections will be dedicated to presenting useful clinical data and to updating the state of the art.

Third, addressing pertinent and pressing problems in basic science, clinical disorders, patient care, medical economics, and medical ethics in four or five annual monographs which will include clinician-oriented contributions from international authorities.

We greet with enthusiasm our new affiliated institutions.

David A. Dreiling, M.D.
Editor-in-Chief

Cedars-Sinai Medical Center, Los Angeles

Cedars-Sinai Medical Center, which is affiliated with the University of California, Los Angeles, School of Medicine, covers an area of 1.6 million square feet in West Hollywood.

History and Introduction

Cedars-Sinai Medical Center traces its history to a small facility for the care of Jewish indigents on the east side of Los Angeles, an institution known as the Kaspare Cohn Hospital which was founded in 1902. By 1913, the hospital had grown to a 100-bed structure. Subsequently it became the Cedars of Lebanon Hospital.

In 1921, a second Jewish hospital, the Mount Sinai Hospital, was established as a six-bed unit in a private home to offer care for the victims of the influenza epidemic. The Mount Sinai facility also grew, becoming a second major Jewish institution serving the Jewish indigent.

The second major phase in the medical center's history was the simultaneous growth of these two independent hospitals—Cedars of Lebanon Hospital (built in 1929) and Mount Sinai Hospital (built in 1955) at new sites west of the original founding institutions.

Cedars of Lebanon Hospital became known not only for its treatment of famous personalities in the entertainment industry, but also for the excellence of its clinical care and research.

In 1961, recognizing the advantages of a single institution to serve the identical missions of the two hospitals, the boards of directors of the Cedars of Lebanon and Mount Sinai hospitals effected their merger into the Cedars-Sinai Medical Center, an institution dedicated to high quality in patient care and to teaching, research, and postgraduate education.

Begun in 1971, the present Cedars-Sinai Medical Center was completed in 1976. It contains 1,120 beds in an area of 1.6 million square feet, and has a staff of over 1,500 physicians and a house staff of over 150. It is affiliated with the UCLA School of Medicine.

Cedars-Sinai Medical Center has had a long history of biomedical research. Associated with the center's medical research institute are, for example, Harry Goldblatt (Goldblatt kidney), Myron Prinzmetal (Prinzmetal angina), and H. J. C. Swan and William Ganz (Swan-Ganz catheter). It has a worldwide reputation in the fields of splenectomy, biliary tract disease (it was the home base of the National Gallstone Study Project), cardiology, and the early treatment of coronary occlusion with streptokinase intracoronary perfusion, to cite only some of its achievements.

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Fibromyalgia: Unusual Historical Aspects and New Pathogenic Insights

DANIEL J. WALLACE, M.D.

Abstract

Fibromyalgia is a form of soft-tissue rheumatism that has primary and secondary components. Primary fibromyalgia syndrome (PFS) is probably a somatization disorder that principally affects the musculoskeletal system. Its manifestations can be clearly differentiated from psychogenic rheumatism, hypochondriasis, or panic disorders. It usually has a gradual onset and is chronic. Some PFS patients in the 1960s who were told they had myasthenia gravis had conversion reactions and responded to anticholinesterase medication. Secondary fibromyalgia may be induced by trauma, infection, stress, or inflammatory or metabolic disorders. Occasionally, it may have an acute onset and be part of a conversion reaction. These concepts are deduced on the basis of analysis of historical experiences during World War II and polio epidemics. A neutrotransmitter chemical imbalance is proposed as a possible etiopathogenetic factor producing fibromyalgia on the basis of some of the presented insights.

The term "fibromyalgia" (or "fibrositis") was first reported in the nineteenth-century German literature (1) and first described and named in the English literature by Gowers (2, 3). Since this disorder lacked clear-cut histological or laboratory abnormalities, its definition and conceptualization has undergone many changes over the last eighty years. Certain historical descriptions of some related medical disorders appear retrospectively to have been representative of secondary fibromyalgia. During this period of time, one subset—"epidemic neuromyasthenia"—which appeared to have an epidemic nature was embraced as a distinct entity and subsequently ignored (4). A second disorder, "myasthenic syndrome" (5), has been described as a subset of myasthenia gravis, and critical examination shows that it is likely to have been fibromyalgia. This paper will review current thinking on what fibromylagia is, place the disorder subsets in their proper perspective, and present new insights about its etiopathogenesis based on historical data.

Overview of Fibromyalgia: Current Concepts

Three excellent reviews concisely express the state of the art as applied to fibromyalgia (6–8). Smythe considers fibrositis to be a pain amplification syndrome with trigger points that tend to occur in 14 areas. Primary fibromyalgia is defined as widespread aching of more than three months duration, local tenderness of 12 of 14 specified sites, skin roll tenderness over the upper scapular region, disturbed sleep with morning fatigue and stiffness, along with normal serologies, sedimentation rates, blood chemistry panels, muscle enzymes, and sacroiliac films without underlying causes such as trauma and osteoarthritis (6).

Bennett considers fibromyalgia to be characterized by an ill-defined musculoskeletal pain, often shifting in location (7). Exacerbation occurs with stress, noise, cold, unaccustomed exercise, or chronic fatigue. Prominent morning stiffness, nonrestorative sleep and poor work tolerance are common features. Normal joint and muscle ex-

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aminations and laboratory findings and depressed affect are found along with trigger points in the upper scapular area and skin roll tenderness. Secondary fibrositis occurs with other rheumatic diseases, certain viral infections, trauma, osteoarthritis, metabolic disturbances, polymyositis, polymyalgia rheumatica, steroid or narcotic withdrawal syndrome, among others, and must be differentiated from psychogenic rheumatism. A follow-up report by Bennett's group documented more axial pain, severer aching and stiffness, morning fatigue, tension headache, irritable bowel syndrome in primary fibromyalgia than in an age-, sex-, and clinic-matched control group (9).

Yunus et al studied 50 patients in exhausting detail who met Smythe's general criteria (8) and evolved their own, more precise definitions. Eighty-six per cent were women; mean age of onset was 29. New criteria were proposed for fibromyalgia, which was renamed "primary fibromyalgia syndrome" (PFS). They included generalized aches and pains or prominent stiffness involving three or more sites (preferably at least five tender points) for at least three months in the absence of secondary causes. In addition, at least five of the following factors should be present: modulation of symptoms by physical activity or weather factors, aggravation of symptoms of anxiety or stress, poor sleep, general fatigue or tiredness, chronic headache, irritable bowel syndrome, subjective swelling and numbness.

The prevalence of fibromyalgia is surprisingly high, making up 4% to 20% of all new rheumatology specialty referrals (8, 10–12). Soft-tissue rheumatism, in the form of secondary fibromyalgia, has been documented to be a major cause of industrial disability (13). Fibromyalgia is a relatively neglected entity and almost no research is being conducted on it. Extrapolations of epidemiologic data suggest that at least 3 million Americans have severe enough fibromyalgia to seek medical attention.

The cause of fibromyalgia is unknown. Very few theories have been proposed and none have been subjected to vigorous scientific inquiry. Nevertheless, it appears that initiating factors are often physical or emotional trauma. Numerous efforts to find consistent histologic abnormalities in fibrositic "nodules" have been unsuccessful. No consistent abnormal laboratory or electromyogram findings are present. Much of the recent research into and resulting hypotheses of pain mechanisms can be applied to fibromyalgia. It is possible that myofascial trigger points arise as a result of endorphin or enkephalin imbalances or tissue ischemia (14). Local factors, such as stresses from loads or poor posture, are said to result in deep hyperalgesia, referred pain, and ultimately spasm (6). Fibromyalgia is also associated with sleep disturbances as a result of documented decreases in non-REM (rapid eye movement) sleep (15).

The treatment of fibromyalgia is aimed at decreasing the symptoms caused by putative etiopathogenetic factors. Medications such as tricyclic antidepressants may raise endorphin stimulation levels, relax patients, and improve sleeping patterns. Analgesics, muscle relaxants, and antiinflammatory drugs modestly improve pain and spasm. Physical measures include coolant sprays, local infiltration of trigger points with anesthetic or corticosteroids, local heat, massage, biofeedback, acupuncture, instruction in good posture habits, TENS units, cervical pillows and restful vacations (16). Unfortunately, controlled studies to demonstrate beneficial effect of these measures are lacking. Until pain mechanisms are better elucidated or pathophysiology is better understood, fibromyalgia management will continue to be a major public health problem.

Proposed Historically Unrecognized Reports of Fibromyalgia

Three sets of reports are retrospectively proposed as describing historically unrecognized fibromyalgia (Table 1). The first two—outbreaks among soldiers in World War II and "epidemic neuromyasthenia"—were acute forms of secondary fibromyalgia, and the third, "myasthenic syndrome," was in reality primary fibromyalgia syndrome (PFS). Although there is certainly a degree of overlap with other disease entities, the author feels that the majority of patients in these groups had fibromyalgia.

Epidemic Fibromyalgia

Outbreaks among Soldiers in World War II. In the 1949 edition of Comroe's *Arthritis and Allied Conditions* (17), Wallace Graham's chapter on fibrositis noted: "Rheumatologists in America were startled in 1940 when Copeman called attention to the high incidence of fibrositis in the British forces." Hollander, who was Comroe's successor as editor, also noted a significant incidence in the American army in his chapter on rheumatologic diagnosis. These observations were included in the 1953 and 1960 editions and deleted subsequently. All times of war, famine, or devastation result in stress and inadequate coping mecha-

TABLE 1

Proposed Historically Unrecognized Reports of Fibromyalgia

Primary fibromyalgia syndrome

Myasthenic syndrome
1. Tether, Indiana University (1961)
2. Johns and McQuillen, Johns Hopkins (1965)
3. Schwab and Perlo, Mass. General (1965)
4. Fullerton and Munsat, UCLA (1966)

Secondary fibromyalgia

Epidemic fibromyalgia
Outbreaks among soldiers in World War II
1. *Arthritis and Allied Conditions* (1949, 1953, 1960)
2. Hutchison (1942) 69% of referrals
3. Savage (1942) 52% of referrals
4. Bach (1947) 71% of referrals
5. Beeson (1942)
6. Boland (1943) 24% of referrals

"Epidemic neuromyasthenia" and the polio epidemics
1. Los Angeles (1934)*
2. Iceland (1948)*
3. Adelaide, Australia (1949)
4. New York (1950)
5. Washington, D.C. (1953)*
6. Copenhagen (1952)
7. Middlesex, England (1952)
8. Coventry, England (1953)
9. Durban, South Africa (1955)*

* Chronicity of symptoms noted in follow-up reports.

nisms, but only during World War II was the fibromyalgia issue addressed specifically. Hutchison reported that in a British army hospital, up to 69% of all rheumatology referrals were for fibromyalgia (18). Most of these soldiers had undergone significant strain and wear and tear and had emotional stress. He noted:

> I have met with instances where men have spent many weeks off duty 'enjoying' physical therapy for fibrositis which was no longer existent and at which stage it had become well-nigh impossible to convince them that they were organically sound and fit for duty. Some cases have been referred to the psychiatrist, but by this stage improvement is difficult to observe within the army.

Savage reported that 141 of 270 rheumatology referrals (52%) at two military hospitals were for fibromyalgia (19). Some were exacerbations of a preexisting industrial fibromyalgia that was prominent among coal miners. Most were accentuated by wearing heavy equipment or by drill. He denied any significant psychiatric problems in his patients and reported marked relief of symptoms by local procaine injections. Bach reported a 71% incidence of fibromyalgia among rheumatology referrals (20). These British physicians were much more aware of fibromyalgia than their American contemporaries but used broadly based definitions and criteria that encompassed PFS, secondary fibromyalgia, strains, bursitis, psychogenic rheumatism, and disc disease. Ellman et al defined fibromyalgia symptoms as being pain (often traveling and aggravated by exertion, cold, and exposure), stiffness, and weakness (with general lassitude and easy fatigability), with normal x-rays and laboratory examinations (21).

The incidence in the American armed forces was much less than in the British (5%–10% of rheumatology referrals) but definitions were much narrower. In addition to Hollander, two other Army doctors who also achieved prominence during the postwar years wrote about fibromyalgia in soldiers. Beeson served with the American Red Cross–Harvard Field Hospital. He described a syndrome characterized by neck and shoulder pain that lasted longer than four days in half (22). He was concerned about transmission of this "contagion" and fruitlessly searched for an etiological agent. He noted that most of those afflicted were white women. Those with fibromyalgia represented 13% of the clerks, 6% of the soldiers, and 23% of the hospital paramedical staff. Boland evaluated 450 consecutive arthritis referrals to his Army hospital and labelled 26 as having fibromyalgia and 92 as having psychogenic rheumatism, of whom he conceded many also had fibromyalgia (23). Psychologic profiles of these two groups revealed six key commonalities: (a) concern over loss of security and separation from loved ones, (b) concern over loss of ability to control one's destiny, (c) resentment of authority especially when invested in persons felt to be inferior, (d) fear of bodily harm, (e) confusion from strange surroundings, crowding, regimentation, and competition, (f) concern for safety and financial well-being of dependents.

"Epidemic Neuromyasthenia" and the Polio Epidemics

A remarkable putative disease entity known as epidemic neuromyasthenia (EN), or benign myalgic encephalomyelitis, was first reported in 1935 and occupied top billing in journals, such as the *New England Journal of Medicine* and the *American Journal of Medicine*, throughout the 1950s with extensive reviews (4, 24, 25). Doubts were first cast upon the existence of this disorder in 1970, and it is now nearly forgotten (26). In retrospect, it appears to have been a potpourri of cases of encephalomyelitis of unknown cause, mass hysteria, and fibromyalgia that presented similarly and were thrown together to create a new disease. The incidence of EN decreased dramatically after polio vaccination became available and many of the outbreaks represent perhaps in retrospect an excellent example of epidemic fibromyalgia.

Los Angeles was struck by a frightful polio epidemic in 1934, and many of these patients were cared for at the Los Angeles County General Hospital (26). During this period, 210 people—nearly all of whom were women—began developing muscle tenderness, hyperesthesia, insomnia, emotional upset, sensory disturbances, localized muscle weakness, and neck and back stiffness. No temperatures above 100° were noted. This group, which eventually included 16% of the student nurses and 8% of the graduate nurses but only 2% of the hospital orderlies, were originally thought to have polio. Thorough investigations failed to turn up any etiologic source or organism. Many of these patients were hospitalized and others left their jobs for months. None of them died. In 1965, Marinacci reported on the long-term sequelae in a group he was able to follow for 30 years and noted that the initial symptoms persisted in a large number of those originally affected (27).

Shelokov details an outbreak of EN among 29 of 41 student nurses at a Washington, D.C. hospital during a polio epidemic in 1953. The symptoms were characterized by stiffness of the back and neck, localized muscular weakness, and tenderness, depression, and diarrhea. Only 1 of 72 hospital patients and 1 of 19 hospital staff physicians were similarly affected. All attempts to isolate an organism were unsuccessful. Spinal taps and all blood determinations were normal. He noted in 1957 that these women often had a prolonged disability and 85% still had symptoms that were especially exacerbated by physical exertion, damp or cold weather, and onset of menstrual periods.

Similar outbreaks were recorded during polio epidemics (4) in Iceland (1948); Adelaide, Australia (1949); New York (1950); Copenhagen (1952); Middlesex (1952) and Coventry (1953) in England; and Durban, South Africa (1955). A follow-up of the Iceland epidemic in 1955 noted that only 25% of the patients had recovered, and 52% still had muscle tenderness. Many still had nervousness, fatigability of muscles, muscle pain, sleeplessness, and loss of memory. At least 11 of the 98 South African patients were still symptomatic in a 1978 report (28). Daikos noted that EN patients responded to physical measures, analgesics, and muscle relaxants but had no response to corticosteroids (29).

TABLE 2

Classification of Some Psychosomatic Disease Manifestations

Somatiform disorders
- Somatization disorder (includes classic hysteria and PFS)
- Hypochondriasis
- Conversion disorder (hysterical neurosis)
- Psychogenic pain disorder (includes psychogenic rheumatism)

Panic attacks or disorder (mass hysteria)

"Epidemic Neuromyasthenia": Fibromyalgia and Hysteria

In his review of EN in 1959, Acheson includes cases that are clearly of different etiologies (4). Probable instances of encephalomyelitis in West Africa and "sporadic" cases of what appears to be fibrositis are included. Other EN reviews have included patients with signs of pharyngeal injection and cervical adenopathy, which clearly represent viral or other infectious processes (30). Acheson's review was the first to raise the issue of hysteria and he ultimately rejected the notion—probably because he was dealing with a heterogeneous series of a variety of disorders. Mass hysteria has occurred throughout history and is notable for causing the bizarre frenzies of St. Vitus' dance in the Middle Ages and the actions of nuns in seventeenth-century France, popularized by Aldous Huxley's *Devils of Loudon*.

Hysteria has often been confused with psychogenic rheumatism, hypochondriasis, panic attacks, and conversion reactions, and these terms must be defined and differentiated from each other.

The latest DSM-III defines psychogenic pain disorders as a somatiform disorder characterized by severe and prolonged pain not due to another mental disorder (31). The pain is inconsistent with the nervous system's anatomic distribution and is noted in the absence of explanatory physical or physiologic findings. Psychogenic factors augment and perpetuate the symptoms including ability to avoid certain activities or responsibilities because of the pain, secondary gain, and a temporal relationship between an environmental stimulus and a related need to exacerbate pain symptoms. Unlike fibromyalgia, no response to analgesics or physical therapy occurs. Yunus' review also carefully differentiates these two entities (8).

Other somatiform disorders include somatization disorder, hypochondriasis, and conversion disorders (Table 2). Somatization disorder occurs almost exclusively in women, usually begins before the age of 30, and consists primarily of multiple somatic problems without adequate explanation (32). The symptoms are chronic and relapsing and do not appear to be under voluntary control. They are often associated with excessive numbers of surgical procedures, anxiety, occupational difficulties, depression, marital discord, histrionic personality, and resulting alteration of life patterns. Even though patients live a normal lifespan, they see themselves as chronically ill, and often are doctor-shoppers. Their problem is unrelated to abuse of drugs (legal or street) or alcohol. Musculoskeletal symptoms are noted (but not elaborated upon in the DMS-III), along with gastrointestinal, psychosexual, cardiopulmonary, and menstrual complaints as well as pain. No fibromyalgia patterns have been described until recently. Marks et al interviewed 18 PFS patients and found that they perfectly fit the somatization disorder criteria (33). He describes fibrositis as a conversion of influences that consist primarily of pain-proneness and somatization. Payne et al compared Minnesota Multiphasic Personality Inventory (MMPI) responses in 30 PFS and rheumatoid arthritis patients. The PFS group had significantly increased comparative scores on both neurotic and psychotic scales (34). Ahles, Yunus et al, however, suggest that only one third of patients are psychologically disturbed (34a).

Hypochondriasis occurs predominantly in middle-aged men and women and consists of normal physiologic sensations being misinterpreted as indicators of disease. This has only a minimal overlap with accepted descriptions of fibromyalgia.

Conversion symptoms (also called hysterical neurosis) are unexplained individual symptoms suggesting neurologic disease (for example, amnesia, paralysis, spells, blindness) that cannot be explained by physical disorders or pathophysiologic mechanisms. They are usually short-lived and often have a good prognosis. They can be part of schizophrenia, affective disorders, neurologic diseases, or somatization disorders (35).

The term "hysteria" has undergone numerous changes in interpretation over the last few years and is now felt to be included in the classification of somatization disorders, the subset of hysterical neurosis being included in conversion symptoms (36).

A subset of PFS can thus be delineated as a somatization disorder clearly differing from psychogenic pain disorders (which include psychogenic rheumatism) and hypochondriasis. Conversion symptoms have never hitherto been described in fibromyalgia but the author proposes that they were the initiating features in the polio-epidemic-associated EN cases described above. Hence, a secondary fibromyalgia may have an acute onset in a minority of cases.

Finally, somatization disorders must be differentiated from panic disorders or panic attacks, which are short-lived disturbances when persons are extremely anxious and have well-known somatic responses to extreme fear manifested by tachycardia, hyperventilation, palpitation, diaphoresis, and paresthesias. McEvedy has made an attempt to differentiate these features (37). He concentrated on an EN epidemic at the Royal Free Hospital in London in 1955 and concluded that it was an example of mass hysteria (which we would now term panic attack). In this particular instance, 300 cases were reported involving 10% of the female and 3% of the male staff. No polio epidemic was in progress and the symptoms were at first "common to the prodromal stage of most infections." However, they quickly assumed prominent features of hyperventilation (40%), hemiplegia, stocking-glove anesthesias, vertigo, and dizziness. This is clearly different from fibromyalgia and was of shorter duration. McEvedy also reviewed reactions in convents and among schoolgirls and concluded that the clinical presentations were similar. Small and Borus recently reviewed several epidemics of mass hysteria, mostly among schoolchildren. No chronicity of any of the symptoms was noted (38).

The author proposes that epidemic forms of fibromyalgia as manifested by paramedical hospital personnel during polio epidemics were brought on by an attempt at a conversion reaction, but in contrast to other outbreaks of panic attacks (mass hysteria) assumed a chronic fibromyalgia mold.

Myasthenic Syndrome

Myasthenia gravis (MG) is a disorder manifested by an abnormal weakness and fatigue of skeletal muscle. A circulating IgG antibody against acetylcholine receptor molecules has been found to be pathogenetic. Until recently, MG was often a difficult diagnosis to make and there was a group of patients who appeared to have atypical myasthenia, or "myasthenic syndrome." Since repetitive stimulation testing and antireceptor antibody determinations have become readily available, the group of patients with "myasthenic syndrome" has practically disappeared. On reviewing the literature from the 1960s on myasthenic syndrome, it is the author's view that many of these patients probably had PFS and were misdiagnosed. This diagnostic error could well be a master stroke of serendipity, because these patients often responded to conventional MG therapies.

JE Tether published a chapter in a 1961 textbook on MG entitled "Mild myasthenic state" recounting his 20 years as head of the MG clinic at the Indiana University Medical Center (39); 2,327 patients were referred to him throughout the state. Of these, 529 were diagnosed as having MG by fulfilling standard clinical criteria and having a positive neostigmine or tensilon and negative curare test; 1,023 were deemed nonmyasthenic, but 775 were said to have a "mild myasthenic state." This group consisted largely of women aged 20 to 40 at diagnosis. The onset of symptoms was gradual but sometimes seemed to follow a traumatic event. Symptoms were exacerbated by exertion, infection, menstruation, and emotion. Common features included fatigue, tightness or stiffness and aching in the back of the neck, chest heaviness, aching in interscapular and lumbar areas, poor postures, and sad, tired expressions. Tether divided "mild myasthenic state" into three classes. Class I was defined as a "mild fatigue state with (a) presenting complaint of pain . . . and slightly subnormal work capacity. No definite myasthenic signs." Class II patients had a pain with unusual fatigability and subnormal work capacities. Even though Class III had occasional diplopia, slight ptosis, and other mild bulbar symptoms, Classes I and II had no real signs of MG and appeared to have had fibromyalgia. All the "mild myasthenic state" patients were treated with pyridostigmine (Mestinon), and—surprisingly—nearly all patients improved with anticholinesterase therapy.

Johns and McQuillen described a group of women at Johns Hopkins who had the "asthenic syndrome" (5). They had complaints of fatigue without objective signs of weakness, bulbar complaints, and ability to tolerate near-lethal doses of anticholinesterase drugs without untoward effects. No dependence to the drugs evolved and no withdrawal syndrome was noted.

Schwab and Perlo studied 120 patients referred to the MG clinic at Massachusetts General Hospital between 1954 and 1964 (40). Forty-nine, or 37.6% of them, were diagnosed as having "chronic fatigue syndrome." Their prominent features were neuroasthenia and asthenic syndrome. The authors wrote: "Not infrequently, patients of this type of fatigue state demonstrate a surprising tolerance to anticholinesterase medication. This phenomenon was considered by the referring physician to be prima facie evidence for the presence of myasthenia."

Fullerton and Munsat studied seven patients who had "pseudo-myasthenia gravis" in detail at UCLA Medical Center (41). All were women, aged 22 to 60. They had an average of fifteen complaints each, including dizziness, headaches, diffuse abdominal discomfort, chest pain, back pain, fatigue, urinary problems, dyspareunia, and dysmenorrhea. They had undergone a surprisingly large number of pelvic operations, and were "doctor-shoppers" until they were given a diagnosis of MG and became attached in a devoted way to the diagnosing physician. Psychiatric profiles revealed strict and repressive family upbringing, hysteria, and marital problems. They developed a conversion reaction simulating MG after this condition was inadvertently suggested to them by their physicians and felt better with anticholinesterase medication.

In summary, this group of patients probably represents a second example of patients with conversion reactions. In this case, their preexisting fibromyalgia symptoms assumed myastheniclike features.

Discussion

First, it is proposed that a subgroup of PFS may be a subset of somatization disorder. It can be clearly differentiated from hypochondriasis and psychogenic pain syndromes. Fibromyalgia usually evolves slowly and displays a chronic, relapsing course. However, secondary fibromyalgia may have an acute onset during times of stress, such as seen during World War II and in polio epidemics. The chronicity of symptoms noted in follow-up reports in the latter circumstance differentiated it from panic attacks or mass hysteria.

A great deal of debate has ensued as to whether fibromyalgia can be induced by trauma. Most rheumatologists have rendered court opinions on one or both sides in automobile accident cases. This confusion arises because of the lack of hard data and general experience that most cases of fibromyalgia have a more indolent onset. The experiences described in this paper imply that a more acute onset is, indeed, probable. Secondly, it is postulated that some patients diagnosed in the 1950s and 1960s as having mild myasthenic syndrome probably had PFS which was preexisting and of chronic onset. Interestingly, when myasthenia gravis was suggested to them as a global diagnosis accounting for all their symptoms, these patients experienced a conversion reaction and even responded to medication given to treat myasthenia gravis.

The first group responded to tricyclic antidepressants, and the second group felt better with anticholinesterase drugs (admittedly in uncontrolled settings). These responses suggest that fibromyalgia could be a disorder of a hitherto undescribed chemical imbalance of neurotransmitters. Central nervous system serotonergic function plays an important role in the regulation of non-REM sleep, pain sensitivity, and affective states. The synthesis of brain serotonin is dependent on the disposition of plasma trytophan (42). Moldofsky and Warsh demonstrated that 8 patients with PFS had plasma free-tryptophan levels that inversely correlated with the severity of subjective pain (43). Imbalances in neurotransmitter dynamics have been implicated in schizophrenia, manic-depressive psychosis, and other behavioral disorders, and drugs which regulate these imbalances are of great therapeutic importance. The author proposes that studies of the etiopathogenesis of PFS should proceed along the same lines. In addition, a controlled study on the use of agents, such as a pyridostigmine in fibrositis, might be justified. Fibromyalgia is a fascinating, misunderstood diagnostic category whose mechanisms are just beginning to be elucidated.

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Parathyroid Hormone Measurements in Hemodialysis Patients as Assessments of Renal Osteodystrophy

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Abstract

We correlated parathyroid hormone concentrations, measured by both aminoterminal (N-PTH) and carboxyterminal (C-PTH) assays, with skeletal x-rays from 31 patients undergoing long-term hemodialysis in order to determine the utility of PTH measurements in assessing renal osteodystrophy. The presence of bone disease was related to the duration of dialysis. Both the N-PTH and C-PTH levels were higher in the sera of patients with bone disease than in patients without radiographic osteodystrophy. All patients without bone disease had N-PTH levels below 1090 pg/mL or C-PTH levels below 6120 pg/mL, whereas 45% of patients with bone disease had N-PTH levels and 50% of patients with bone disease had C-PTH levels above these respective values. All patients with severe bone disease ($N = 7$) had elevated N-PTH concentrations; only 5 of the 7 severe-bone-disease patients had elevated C-PTH levels. Although neither test was sensitive for the presence of bone disease, markedly elevated N-PTH levels were a good indication of severe bone disease in all patients studied.

Chronic renal failure results in major derangements of normal calcium homeostasis. As glomerular filtration decreases, phosphate retention, end-organ resistance to parathyroid hormone, and decreased production of the active metabolite of Vitamin D, 1,25-dihydroxycholecalciferol, develop (1–3). This leads to the development of hypocalcemia and, subsequently, secondary hyperparathyroidism. The undesirable clinical effects that may result from parathyroid hyperplasia include hypercalcemia, soft tissue calcifications, pruritus, possibly uremic neuropathy, and different types of metabolic bone disease known collectively as renal osteodystrophy (3, 4).

After secretion, endogenous parathyroid hormone (PTH) is rapidly metabolized into biologically active N-terminal fragments and biologically inactive C-terminal fragments (5). Since the clearance rate of the C-terminal fragments depends on renal function and these fragments are elevated in the sera of patients with renal insufficiency, PTH measurements by assays with C-terminal specificity may not accurately reflect parathyroid function in chronic renal failure (5–7). The N-terminal fragments and intact PTH molecule are not solely dependent on renal function for metabolism, and, therefore, measurement of PTH concentrations with an N-terminal specific assay may provide a more accurate index of parathyroid activity in chronic renal failure and renal osteodystrophy. In the present study, we examined patients with chronic renal failure and varying severity of metabolic bone disease in order to correlate several clinical and laboratory parameters of renal osteodystrophy with PTH measurements made by both N-terminal and C-terminal PTH assays.

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Materials and Methods

Patients. Thirty-one patients with chronic renal failure undergoing regular maintenance hemodialysis were studied. Eleven patients received therapeutic doses of 1,25-dihydroxycholecalciferol (Rocaltrol), while 20 patients did not receive Vitamin D supplementation. Blood was obtained from the vascular shunt just prior to dialysis. The serum was rapidly separated and frozen at −20°C until assay. Radiologic films of the skull, chest, pelvis, and hands were examined by ourselves and independently by radiologists not involved in this study. In the event of conflicting interpretations, a second, independent radiologist's opinion was obtained. We used a grading scale of zero to three as an index of the severity of metabolic bone disease. Patients with no bony abnormalities on x-ray were graded zero (n = 11), those with vascular or soft-tissue calcifications were graded one or two (mild to moderate, n = 13), and those with erosions were graded three (severe, n = 7). In this study, no patients demonstrated pathologic fractures.

Biochemical Measurements. The following assays were performed on serum, using an autoanalyzer (Alpken, Calckamas, Ore.): inorganic phosphorus, total protein, alkaline phosphatase, 5′-nucleotidase, gamma glutamyl transpeptidase, creatinine, and urea nitrogen. Serum protein electrophoresis was performed on cellulose acetate strips. Total calcium and magnesium were measured by atomic absorption (8) and ionized calcium was determined using a calcium-specific electrode (Orion Instruments, Cambridge, Mass.); pH and temperature corrections were applied to the results. C-PTH and N-PTH assays were performed as previously described (9, 10). Determination of 25-hydroxycholecalciferol was by competitive protein-binding following extraction and purification by LH20 column chromatography (11); 1,25-dihydroxycholecalciferol was assayed by competitive binding using rachitic chick intestine cytosol following extraction, solvent partitioning, and high-performance liquid chromatographic purification (12). All assays were performed at BioScience Laboratories, Van Nuys, Calif.

Statistics. Spearman's rank order correlation coefficient was used to determine correlation coefficients between various biochemical parameters. The data were analyzed for all patients and separately for the subgroup of patients receiving (n = 11) and the subgroup of patients not receiving (n = 20) Vitamin D supplementation. The patients were classified as having no bone disease, mild-moderate bone disease, or severe bone disease. A Kruskal-Wallis One-Way ANOVA was used to determine if there were any significant differences between these three groups with respect to the various biochemical variables and number of years on dialysis. To determine which groups differed, multiple comparisons were performed using Fisher's Least Significant Difference method (13). The alpha level was set at 0.05 for these comparisons. A similar comparison of the biochemical and clinical variables in the patients categorized into two groups (bone disease present vs bone disease absent; patients receiving Vitamin D supplementation vs patients not receiving Vitamin D supplementation) was carried out with the Mann-Whitney U-test for all tests. A P value less than or equal to 0.05 was considered to be statistically significant for all tests.

Results

Several differences were noted between patients with and without radiographic renal osteodystrophy (Table 1). Patients without bone disease had been on dialysis for significantly less time than those with mild bone disease; the difference between patients without and those with severe bone disease was not significant. Significantly higher concentrations of serum alkaline phosphatase, N-PTH, and C-PTH were found in patients with severe bone disease than in those with no or mild-moderate bone disease. But no significant differences in the concentrations of these analytes existed between the mild-moderate and no bone disease groups. When the patients were grouped into two categories, those with and those without bone disease, patients with bone disease had been on dialysis significantly longer and had significantly higher concentrations of alkaline phosphatase and gamma GT levels. No other significant differences were found in this comparison. The absence or presence of Vitamin D supplementation had no effect on the variables compared in this analysis. Although patients receiving 1,25-dihydroxycholecalciferol had higher serum concentrations of this Vitamin D metabolite in their blood (mean, 20.2 pg/mL) than did patients not receiving the drug (mean, 9.9 pg/mL), the difference was not statistically significant.

N-PTH, C-PTH, and total calcium concentrations were examined in all patients in order to explore the utility of PTH assays in predicting the presence of bone disease and to ascertain whether the two assays provide different kinds of infor-

TABLE 1

*Clinical and Biochemical Differences in Patients with and without Radiographic Renal Osteodystrophy**

Bone disease	Years on dialysis mean ± SD	Alkaline phosphatase mean ± SD U/dl	N-PTH mean ± SD pg/ml	C-PTH mean ± SD pg/ml
None (n = 11)	1.55 ± 1.13	88.8 ± 48.1	453 ± 212	3797 ± 774
Mild (n = 13)	3.60 ± 1.88	117.5 ± 68.5	452 ± 454	8689 ± 10191
Severe (n = 7)	3.07 ± 1.72	219.3 ± 114	1720 ± 544	15967 ± 10287
Significance Category	none < mild	none < severe mild < severe	none < severe mild < severe	none < severe mild < severe

* $p < 0.05$ by Kruskal-Wallace and Fisher's Least Significant Difference tests.

mation in renal-failure patients on hemodialysis. Fig. 1 illustrates the relationships. In order to define the utility of these assays in detecting bone disease, the mean and standard deviations were calculated for the N-PTH and C-PTH results from the hemodialysis patients without radiographic evidence of renal osteodystrophy. The value of the mean plus three standard deviations was used as a discrimination level in order to provide increased specificity in this diagnostic setting. For N-PTH, this value was 1090 pg/mL, and for C-PTH it was 6120 pg/mL. None of the patients without bone disease had concentrations at or above these levels (100% specificity). In the N-PTH assay, 9 of 20 (45%) of the patients with bone disease (2/13 with mild and 7/7 with severe) had concentrations above the mean plus 3 SD, while 10 of 20 (50%) of these patients (5/13 with mild and 5/7 with severe) had C-PTH concentrations above the discriminant level. Thus, neither test was particularly sensitive to the presence of bone disease, whereas both, particularly N-PTH, were good indicators of severe bone disease.

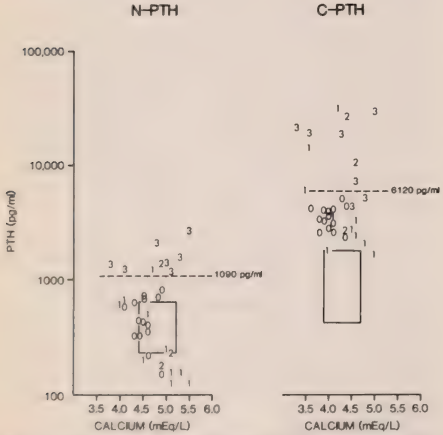

FIG. 1. Relationships between serum and N- and C-terminal PTH concentrations and serum calcium in hemodialysis patients with varying severity of bone disease. Boxes represent PTH-calcium reference ranges in normal controls. Broken lines represent mean plus 3 SD for PTH measurements in hemodialysis patients without bone diseases. Abbreviations: 0 = no bone disease, 1 = mild bone disease, 2 = moderate bone disease, 3 = severe bone disease.

Another interesting point elucidated in Fig. 1 is the relationship between PTH and total calcium concentrations in these two assays. When PTH results below the discrimination levels described above were combined with total calcium values in a regression analysis, a significant correlation existed only with N-PTH ($r = -0.606$, $p < 0.005$).

The correlation coefficients that were significant for the entire group of patients or for at least one of the Vitamin D subgroups are listed in Table 2. Items 1–11 were significantly correlated when all patients were examined together; items 12–18 exhibited significance in only one of the two subgroups of patients. Four correlations were significant in all patients and both subgroups: total calcium vs. ionized calcium, total calcium vs. alkaline phosphatase, 5′-nucleotidase vs. gamma GT, and N-PTH vs. C-PTH. Another correlation of note is that between alkaline phosphatase and N-PTH in the entire group of patients and those patients who were not receiving Vitamin D, supporting a link between N-PTH levels and bone turnover in these patients.

Discussion

The serum concentration of N-terminal and C-terminal PTH fragments depends upon the amount directly secreted by the parathyroid glands or produced in the liver or kidney by the metabolism of intact PTH, and the rate of disappearance from the blood (5). The C-terminal fragment of PTH is cleared by the kidney through both glomerular filtration and tubular reabsorp-

TABLE 2

Significant Parameter and Analyte Correlations

		Correlation coefficients		
		All patients (N = 31)	No Vit D (n = 20)	Vit D Rx (n = 11)
1. Total calcium	vs. ionized calcium	0.6572††	0.5530*	0.8670††
2. Total calcium	vs. alkaline phosphatase	0.6176††	0.5973†	0.6789*
3. 5′nucleotidase	vs. gamma GT	0.7754††	0.7199††	0.8469*
4. N-PTH	vs. C-PTH	0.8264††	0.8662††	0.7745†
5. Years on dialysis	vs. creatinine	0.4903*	0.5589*	0.4117 (N.S.)
6. Alkaline phosphatase	vs. N-PTH	0.3973*	0.4680*	0.2506 (N.S.)
7. Alkaline phosphatase	vs. gamma GT	0.4847*	0.6237*	0.3604 (N.S.)
8. Phosphate	vs. BUN	0.4874*	0.5951*	0.2703 (N.S.)
9. Creatinine	vs. BUN	0.5814†	0.7706††	0.3784 (N.S.)
10. Ionized calcium	vs. alkaline phosphatase	0.4172*	0.3020 (N.S.)	0.6818*
11. Total calcium	vs. BUN	0.4260*	0.3606 (N.S.)	0.1835 (N.S.)
12. Years on dialysis	vs. ionized calcium	−0.2780 (N.S.)	−0.4603*	0.0047 (N.S.)
13. Years on dialysis	vs. 5′nucleotidase	0.3003 (N.S.)	0.5947*	−0.6175 (N.S.)
14. Alkaline phosphatase	vs. 1,25-OH_2D_3	0.1258 (N.S.)	0.4913*	−0.3574 (N.S.)
15. Phosphate	vs. creatinine	0.3052 (N.S.)	0.5147*	−0.1071 (N.S.)
16. 5′nucleotidase	vs. C-PTH	−0.0511 (N.S.)	0.3175 (N.S.)	−0.7857*
17. Gamma GT	vs. C-PTH	−0.0618 (N.S.)	0.2822 (N.S.)	−0.7568*
18. BUN	vs. magnesium	0.3889 (N.S.)	0.0516 (N.S.)	0.7909*

*$p < 0.05$; †$p < 0.005$; ††$p < 0.001$; N.S. = $p > 0.05$

tion (5). Thus, it has been difficult to interpret C-PTH levels in renal failure. Reiss and co-workers (14) found elevated C-PTH levels in some patients with creatinine clearances greater than 70 ml/min. In contrast, Hawker and DiBella (15), using an assay that was specific for intact PTH, found that PTH did not rise in renal-failure patients until the creatinine clearance fell below 20 ml/min. Furthermore, they found that the intact PTH molecule fell when clinical improvement occurred following the administration of exogenous 25-hydroxylcholecalciferol, whereas the change in C-PTH levels was inconsistent. In our study, we found C-PTH levels to be higher in absolute terms than N-PTH levels (Fig. 1). C-PTH levels nearly always exceeded the reference interval, but the majority of the N-PTH levels did not exceed the reference interval established from normal controls. This is in contrast to data from Simon and Cuan (10), who studied 17 patients with chronic renal failure and found that the majority had elevations above the reference interval in both the C-PTH (13/17) and N-PTH (11/17) assays. Our study also demonstrated a good correlation between C-PTH and N-PTH concentrations despite their absolute differences. However, only N-PTH was correlated with alkaline phosphatase levels and showed the normal physiologic (inverse) relationship to total serum calcium in patients without severe bone disease.

Renal osteodystrophy, which consists of varying combinations of osteomalacia and osteitis fibrosa, results in significant morbidity in chronic renal failure patients and in our study was found to be related to the length of time on dialysis and the degree of elevation of serum alkaline phosphatase. Indeed, others have found that the frequency of radiologic renal osteodystrophy is directly related to the duration of uremia and dialysis (16,17). Serum alkaline phosphatase concentrations have been shown to be significantly correlated with osteoblastic surface area in bone biopsies obtained from both dialyzed and nondialyzed uremic patients (18). The correlation in our patients between alkaline phosphatase and gamma GT, a liver enzyme, suggests that the origin of the alkaline phosphatase in these patients involves the liver as well as bone and intestine (19).

Mason and co-workers (20) correlated a number of biochemical parameters in 24 patients with chronic renal failure who were not on dialysis. They noted that three Vitamin D metabolites (25-hydroxycholecalciferol, 24,25-dihydroxycholecalciferol, and 1,25-dihydroxycholecalciferol) were significantly lower in uremic patients than in normal controls and that the 1,25-dihydroxycholecalciferol metabolite was negatively correlated with the serum creatinine and inorganic phosphorus. The severity of osteomalacia determined by histometric evaluations of bone biopsies was negatively correlated with 24,25-dihydroxycholecalciferol and 25-hydroxycholecalciferol concentrations, while the severity of osteitis fibrosa was negatively correlated with 1,25-dihydroxycholecalciferol and positively correlated with immunoreactive PTH. In our study, the Vitamin D metabolites 25-hydroxycholecalciferol and 1,25-dihydroxycholecalciferol were not found to correlate with the severity of bone disease assessed radiographically.

Some of our dialysis patients were treated with synthetic 1,25-dihydroxycholecalciferol (Rocaltrol). This therapy has been demonstrated to directly suppress PTH secretion in the rat (21), although in a clinical study (22) the suppression of PTH appeared to correlate more closely with the rise in serum calcium. In comparing those of our patients treated with 1,25-dihydroxycholecalciferol and those who were not so treated, we found that all treated patients had either no bone disease or mild-moderate bone disease, all were normocalcemic, and none had a PTH level above our discrimination level in either assay. Since the number of patients is low and no controls for length of time on 1,25-dihydroxycholecalciferol therapy or changes in bone disease or PTH concentrations in these patients are available, this information should be interpreted with caution. The correlation matrices for 1,25-dihydroxycholecalciferol treated patients demonstrated a significant negative correlation between C-PTH and both 5′-nucleotidase and gamma GT, while there was a positive correlation between BUN and magnesium. These correlations were not seen in patients who did not receive Vitamin D, and the significance of the correlations is not clear at this time.

We found that there was minimal overlap between the serum concentrations of PTH measured in the N-PTH assay between patients with severe and mild bone disease and no overlap between patients with severe and no bone disease. The serum PTH concentrations measured with the C-PTH assay yielded considerable overlap between patients with severe, mild, and no bone disease. It is of interest that recently Endres and coworkers (23) evaluated 34 patients with chronic renal failure by measuring C-PTH and N-PTH and correlated the serum concentrations with quantitative histomorphometric parameters in bone biopsies. They found that N-PTH assay allowed better discrimination of patients with osteitis fibrosa or mixed lesions from those without bone disease or with mild bone disease or osteomalacia than did their C-PTH assay. Both our data and that of Endres indicate that neither the N-PTH assay nor the C-PTH assay is sufficiently sensitive to justify its use for the detection of bone disease. Radiologic examination or bone biopsy are more appropriate tools for detecting bone disease. The value of PTH assays in this patient population appears to be in assessing the severity of bone disease, and both the C-PTH and the N-PTH assays may be used for this purpose. The N-PTH assay appears to be more sensitive (100% vs. 71%) and specific (78% vs. 50%) for severe bone disease than does the C-PTH assay.

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Elastofibroma Dorsi

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Abstract

Elastofibroma dorsi is a rare tumor of the chest wall caused by excessive production of elastic tissue by fibroblasts. Its characteristic location anterior to the scapula has led some authors to believe that friction between the scapula and the chest wall may operate in its occurrence. The surgical significance of elastofibroma dorsi lies in the possibility of confusing it with a malignant chest-wall tumor, resulting in needless resection of the chest wall.

Only 59 cases of elastofibroma dorsi have been reported in the literature since this lesion was first described in 1961 by Jarvi et al (1). Typically discovered as an incidental finding during thoracotomy, it is usually located between the costal surface of the scapula and the chest wall and is fixed to the extrathoracic fascial layers and to periosteum. These latter features may lead one to believe that the lesion is locally invasive, whereas in fact it is entirely benign. We report this case because of the rarity of the lesion and to emphasize that resection of the chest wall is not indicated for its definitive removal.

Case Report. A 72-year-old white man was referred for evaluation because of an abnormal chest roentgenogram. A mass had been noted in the right postero-inferior lung field in August 1976 when the patient was evaluated for treatment of benign prostatic hyperplasia. His last known normal chest roentgenogram was in 1972. The patient had been a heavy smoker (165 pack-years) and had a chronic nonproductive cough. He reported no hemoptysis, weight loss, or shortness of breath. The history and review of systems were unremarkable.

On admission, his blood pressure was 120/70 mm Hg, his pulse 88, his respirations 20. The remainder of the physical examination was unremarkable. The referring physicians felt that the mass seen on x-ray had increased in size since 1976. We were not convinced of this and transbronchial biopsy of the mass was attempted in order to avoid unnecessary thoracotomy. Although lung tissue was obtained, it was nondiagnostic. At thoracotomy, extensive plaquing of the parietal pleura was found, extending from the sixth rib to the diaphragm posterolaterally. In addition, there was thick plaquing of the visceral pleura on the posterolateral aspect of the right lower lobe, corresponding in position to the mass seen on chest roentgenogram. The diagnoses of these lesions were chronic pleuritis, collagenous pleural plaques, and subpleural interstitial fibrosis.

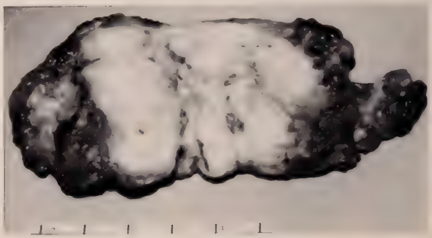

FIG. 1. Central, circumscribed, unencapsulated, white area represents tumor in bisected tissue specimen. It had a fibrous, slightly resilient consistency. Darker areas are surrounding fibroadipose tissue.

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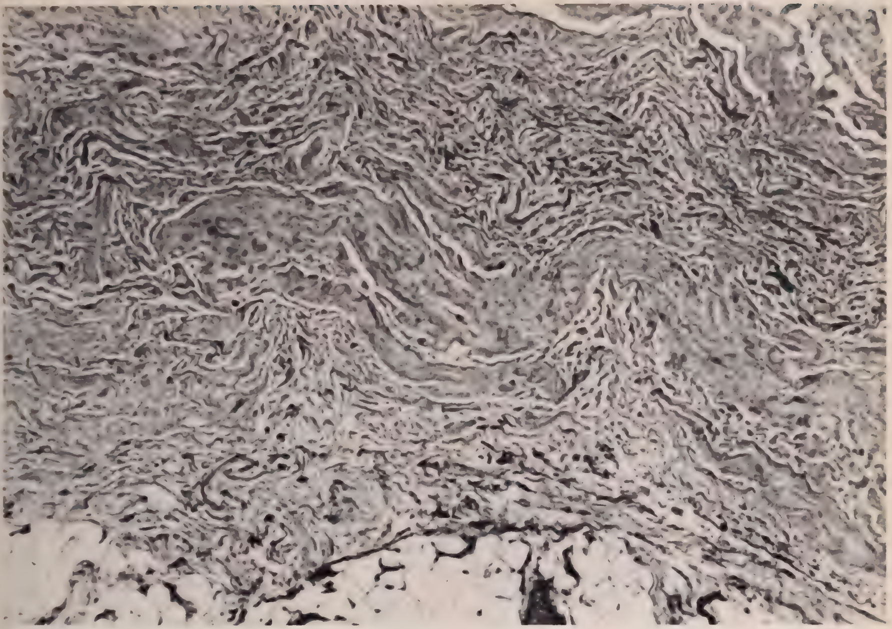
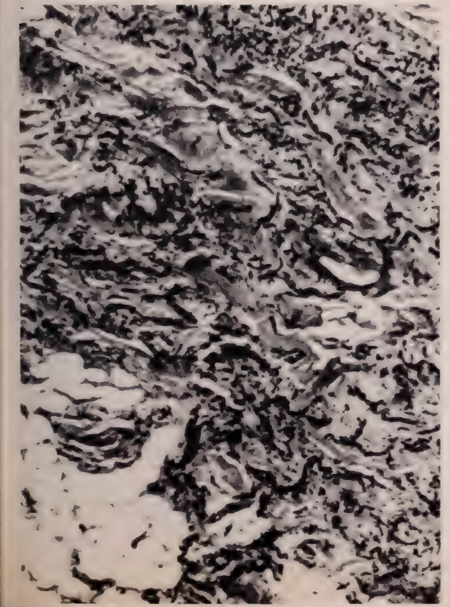


FIG. 2. Tumor, in upper portion of photomicrograph, is made up of varying-sized bundles of collagen and elastic fibers. There is a small amount of fat at the lower edge of the field (H. & E. × 105).

As an incidental finding during the thoracotomy incision, a soft, ill-defined mass was noted between the costal surface of the scapula and the chest wall, extending from the third to the sixth ribs (Fig. 1). Although it was attached firmly to the chest wall, it did not appear to extend through it. The mass was excised widely along with un-



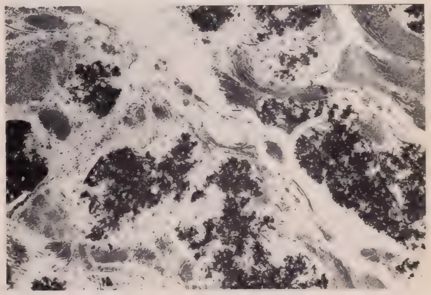


FIG. 3. **Left** Special elastic stain emphasizes elastic nature of many fibers in tumor. Note marked fragmentation and globule formation of elastic tissue (elastic Van Gieson × 105).

FIG. 4. **Above** Electron micrograph from area of elastic fibers seen in H. and E. sections. Amorphous electron-dense areas represent elastic tissue component. Numerous lighter-appearing collagen fibers are also seen (× 8000).

derlying periosteum and some intercostal muscle. Frozen section revealed fibrofatty tissue. The histologic diagnosis on permanent sections was elastofibroma dorsi (Figs. 2–4). The tumor was composed of bundles of collagen and elastic fibers. The elastic fibers, as seen with Van Gieson's elastic strain, demonstrated fragmentation and disarray of the elastic fibers. Ultrastructure of the tumor revealed numerous amorphous electron dense areas representing elastic tissue. The patient remains well without evidence of recurrence fourteen months following surgery.

Discussion. Elastofibroma dorsi was the subject of a recent review by Peters et al (2). The tumor usually appears in women from the fifth to the eighth decades. It is slow-growing, usually right-sided, occasionally bilateral, and is not known to have a familial occurrence. A relationship to trauma and occupational stress has been suggested, but not definitely established (3).

Although rarely reported over the ischial tuberosity, greater trochanter, and in the deltoid muscle, elastofibroma dorsi characteristically appears between the costal surface of the scapula and the chest wall. Infrequently palpable on physical examination, the tumor is usually found incidentally during thoracotomy, as in the present case.

The etiology of elastofibroma dorsi is controversial. Stemmerman et al (4) suggested the etiology to be an elastotic degeneration of collagen. Jarvi et al (3), in an electron-microscopic and histochemical study of elastofibroma, considered it to be a degenerative pseudotumor in which hypertrophy of the elastic tissue was followed by degeneration into segments and globules which gradually underwent absorption. These authors noted, also, an increase in the amount of collagen, including a perivascular accumulation which, they postulated, caused compression of capillaries and precapillaries, causing ischemia and further scarring. Friction of the scapula on the chest wall was mentioned as an aggravating factor, but not proved as such. Indeed, if this were the case, one would expect elastofibroma to be a more frequent occurrence than it is.

The ultrastructure of elastofibroma has been examined more recently by Akhtar et al (5). These authors have demonstrated that the elastic tissue found in elastofibroma is the result of excessive production of elastic material by fibroblasts, and not the result of elastotic degeneration of collagen. Indeed, both collagen and elastic tissue are derived from precursors secreted by the fibroblast.

The surgical significance of elastofibroma lies in not confusing it with a malignant chest-wall tumor. The characteristic location of the elastofibroma, its soft rubbery feel, and its lack of distinct borders should offer clues to its true nature. The presence of pain or tenderness, rapid growth, and specific radiologic characteristics should serve to differentiate malignant chest-wall tumors from elastofibroma and thereby abort needless radical resection of the chest wall.

Acknowledgments

The authors thank Dr. Mikund Shah for referring this patient.

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Laboratory Testing on Admission to a Teaching Service: Expectations and Outcomes for Serum Electrolytes

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Abstract

The high cost of laboratory services has prompted the study of many different methods for modifying the way in which physicians use laboratory tests. However, few studies have been done on the causes of excessive laboratory use. Since there is little evidence that admission screening has any value, we studied the reasons for the measurement of serum chemistries on patients admitted to the inpatient service of a community teaching hospital. We found that most of our residents were motivated by the belief that their patients would benefit from these studies. In addition, we found that the house staff were only 73% accurate in predicting the outcome of specific tests on the basis of a history and physical examination alone and that 26% of outcomes were thought to be highly unlikely (<50% probable) at the time the studies were ordered. These observations suggest that the use of admission chemistries is reinforced by the high rate of unanticipated test results. We do not believe that such behavior should be discouraged unless there is some way to assure a more accurate assessment of patient risk.

Laboratory charges now account for up to 25% of the cost of hospitalization in the United States. In an effort to contain these costs, many investigators have studied methods for modifying the way in which physicians use laboratory tests (1, 2). These studies have employed financial incentives (3), arbitrary limits on the number of tests permitted in a single day (4), reference manuals of laboratory charges (5), educational programs (6, 7), concurrent chart reviews by senior physicians (3), and feedback to individual physicians of the laboratory charges incurred by their patients (5, 8, 9). However, despite the variety of techniques employed, the most successful programs have required an intensive commitment of time and effort (3, 6). Moreover, certain studies using financial incentives (3) and educational programs (7) showed a high rate of recidivism when the interventions were discontinued. These observations suggest that the factors responsible for excessive laboratory use are difficult to modify and therefore deserve closer study.

We felt that it would be valuable to study the reasons for the use of certain diagnostic tests at a large community teaching hospital. We were most impressed by the large number of our house staff who routinely measure serum electrolytes on patients admitted to our inpatient service. Since there is little evidence that admission screening has any value (10, 11), we sought answers to the following questions: (a). What are the physician's reasons for ordering these tests? (b). Do these tests provide information that is otherwise unavailable to the physician? (c). Should this practice be discouraged by an institutional program of behavioral modification? We believe that the results of this study have important impli-

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cations for future research in laboratory cost containment.

Methods

Cedars-Sinai Medical Center is a 1,100-bed acute-care teaching hospital serving the community of West Los Angeles. The medical center is formally affiliated with the University of California, Los Angeles, School of Medicine and provides training for 68 residents in internal medicine. The Department of Medicine has responsibility for a coronary care unit, a medical intensive care unit, a respiratory care unit, a diabetic unit, and a general medical teaching service. Patients with a wide variety of diseases are admitted to the 128-bed general medical service and constitute the population of patients upon which this study is based.

Any patient admitted to this service was eligible for inclusion in this study if the admitting resident or student ordered one or more of the following studies as part of the routine admission procedure: serum sodium, potassium, chloride, bicarbonate, calcium, magnesium, or phosphorus. No panel testing was available at our institution during the period of study, and each of these tests required a separate order. At the time they wrote the admitting orders, house officers were asked to complete a questionnaire that had been included in the patient's admission packet. Each physician was asked (a) to estimate the probability that a significant abnormality would be found among the tests he or she ordered; (b) to predict which of these studies would be abnormal; and (c) to select any number of prepared statements that best represented the reasons for ordering the tests. Space was allotted for a written response as well, but separate reasons for each test were not solicited. The questionnaires were collected the morning after admission.

Patients were excluded from the study in the following circumstances: (a) the patient was transferred to the teaching service from another in-patient service of the medical center; (b) the house officer saw the results of the admission studies prior to completing the questionnaire; or (c) the chart was unavailable for review. The full-time faculty encouraged compliance with the study protocol during daily resident intake rounds.

The medical records of all patients were reviewed by one of the authors subsequent to the patient's discharge. Data pertaining to each patient were recorded on standard forms in order to facilitate computer analysis. The chart review sought the following information: "relevant" diagnoses, the number of admission chemistries ordered and the extent of their abnormality, the number of repeat studies, and the physician's response to the results of the tests. A relevant diagnosis was defined as any disease that was commonly associated with an electrolyte disturbance and was limited to a list of cardiac, renal, hepatic, gastrointestinal, and endocrine diseases chosen at the start of the study. These diseases were further categorized according to the time of diagnosis. A "preadmission" diagnosis was any diagnosis that antedated the symptoms that brought the patient to the hospital. An "admission" diagnosis was any new diagnosis that was made between the onset of symptoms and the end of the second hospital day. A "late" diagnosis was any new diagnosis that was made between the third and the last hospital day.

All laboratory tests were performed in the hospital laboratory according to standard procedures. The referent ranges for our laboratory are as follows: for serum sodium, 135-145 mEq/L; for serum potassium, 3.5-5.0 mEq/L; for serum chloride, 95-105 mEq/L; for serum bicarbonate, 24-32 mEq/L; for serum calcium, 8.3-10.7 mg/dl; for serum magnesium, 1.8-2.9 mg/dl; and for serum phosphorus, 2.5-5.0 mg/dl. A laboratory value was considered biochemically abnormal if it exceeded its referent range.

The definition of a clinical abnormality was based upon a poll of the physicians who were most familiar with the day-to-day operation of the medical service. This group consisted of 3 faculty members (including authors AGE and GHM) and 3 fellows in general internal medicine. No criterion was adopted unless it was presented to and approved by all members of the group. A clinical abnormality was defined as any biochemical abnormality that was sufficiently severe to elicit a significant response from a physician involved in the patient's care. The following were thought to be significant responses. (a) A written response occurred whenever any physician recorded a new diagnosis of an electrolyte disorder, assigned a problem number to an electrolyte disorder, or attempted to explain the laboratory result in progress notes. (b) A therapeutic response occurred whenever the patient was given a form of therapy that would correct the abnormality in question. Taken as evidence of a clinical abnormality were, for hypernatremia, an intravenous rate greater than 124 cc/hr; for hyponatremia, fluid restriction to less than 1500 cc/d, hypertonic saline infusion, peritoneal dialysis, hemodialysis, or an intravenous rate greater than 124 cc/hr; for hyperkalemia, dietary potassium restriction, peritoneal dialysis, hemodialysis, sodium bicarbonate therapy, Kayexelate therapy, an intravenous diuretic, or a glucose/insulin infusion; for hypokalemia, addition of potassium to maintenance intravenous doses, stat oral or intravenous potassium administration, or a maximum standing order for potassium greater than 39 meq/d; for an elevated serum bicarbonate, acetazolamide therapy, hydrochloric acid infusion, ammonium chloride infusion, arginine hydrochloride infusion, or any treatment for significant hypokalemia; for a low serum bicarbonate, sodium bicarbonate therapy, peritoneal dialysis, or hemodialysis; for hypercalcemia, an intravenous diuretic or an IV rate greater than 149 cc/hr; for hypocalcemia, vitamin D therapy, calcium supplementation, magnesium supplementation, peritoneal dialysis, or hemodialysis,; for hypermagnesemia, peritoneal dialysis or hemodialysis; for hypomagnesemia, magnesium supplementation; for hyperphosphatemia, peritoneal dialysis or hemodialysis; and for hypophosphatemia, phosphate supplementation. Hyperchloremia was deemed clinically significant if it was associated with either hypernatremia or a metabolic acidosis that was sufficiently severe to be treated. Hypochloremia was thought to be clinically significant if it was associated with either hyponatremia or hypokalemia that was sufficiently severe to warrant therapy. No cases of diabetic ketoacidosis were admitted to the general medical service during this study.

Statistical Methods. Differences in response rates between physician groups were tested by chi-square analysis or by Fisher's exact test. Differences in physician response to normal and to abnormal laboratory results were tested by chi-square analysis. Contingency analysis was used to examine the proportions of abnormal patients in different prognostic categories.

Results

During the 16 weeks of study, 631 patients were admitted to the general medical teaching service of Cedars-Sinai Medical Center. The admitting house officer measured at least one serum chemistry in 534 (or 84.6%) of these patients. Many of the remaining 97 patients had these studies performed in the emergency room.

All of the criteria for entry into this study were met by 519 patients. However, in 107 cases (20.6% of those eligible), the house officer who wrote the admitting orders failed to complete the questionnaire. No ward team was found to be particularly negligent in this regard, and no house officer was involved in more than 12 (or 11.2%) of these 107 cases.

TABLE 1

Physician Response by Year of Training

Status	No. in patient care	No. responding	No. of responses	Mean (±S.D.) per responder
Medical student	37	22	61	2.27 (±1.64)
Resident				
I	49	48	295	5.88 (±5.33)
II or III	34	20	40	1.95 (±1.36)
Status unknown			16	
TOTALS	120	90	412	4.58 (±4.43)

Data collection was complete in the remaining 412 patients. Table 1 shows the status and number of physicians who participated in this

TABLE 2

Relevant Diagnoses

	Preadmission diagnoses	Admission diagnoses	Late diagnoses
Electrolyte disorders			
Hypercalcemia	1	5	0
Hyperkalemia	3	6	1
Hyperphosphatemia	0	3	0
Hypokalemia	3	15	4
Hypomagnesemia	0	0	1
Hyponatremia	3	11	6
Hypophosphatemia	0	2	1
Metabolic acidosis	1	6	3
Metabolic alkalosis	0	3	3
Respiratory acidosis	0	1	0
Respiratory alkalosis	0	3	0
No. of patients with electrolyte disorders	11 (2.67%)	39 (9.47%)	15 (3.64%)
Other relevant diseases			
Acute renal failure	0	1	1
Ascites	2	8	1
Azotemia	4	7	4
Congestive heart failure	61	16	5
Chronic renal failure	22	1	1
Dehydration	0	10	2
Diarrhea	4	21	0
Diabetes mellitus	45	0	3
Edema	5	19	1
Hematuria	0	9	2
Hypertension	127	4	1
Hyperadrenalism	1	0	0
Hyperparathyroidism	1	0	0
Hyperthyroidism	7	0	1
Hypoadrenalism	3	0	0
Hypoaldosteronism	0	0	1
Hypothyroidism	25	2	1
Hypovolemia	0	1	0
Liver disease	27	17	7
Proteinuria	6	4	2
Renal disease	19	1	6
Renal failure	5	5	7
SIADH	0	0	1
Vomiting	0	32	0
No. of patients with any relevant diagnosis	238 (57.8%)	145 (35.2%)	53 (12.9%)

TABLE 3

Physicians' Reasons for Obtaining Admission Studies

	No. of times reason chosen
Patient-related	
1. There are certain historical features, physical findings, diagnoses or medications that increase the likelihood of an electrolyte abnormality in this patient.	243 (59.0%)
2. The study serves as a baseline in case of changes in the patient's fluid or electrolyte status.	177 (43.0%)
3. I need these studies to direct in-patient therapy.	139 (33.7%)
4. There is nothing to suggest an electrolyte abnormality in this patient, but the yield of electrolyte testing is still sufficiently high to warrant the study.	51 (12.4%)
5. The study would confirm an abnormal result on a previous study.	24 (5.8%)
Physician-related	
6. Somebody else wants these studies.	85 (20.6%)
7. Testing carries no significant risk to patient and is reasonably inexpensive.	24 (5.8%)
8. Failure to order them is a significant malpractice risk.	17 (4.1%)
9. I ordered them for academic interest or purposes.	14 (3.4%)
10. There is no specific reason other than tradition or habit.	4 (1.0%)
Other	12 (2.9%)

survey. Since the questionnaire was directed at the physician who wrote the admitting orders, the study was not intended to survey the attitudes of many medical students or senior residents. Accordingly, the number of responses from these groups was small, and a significant number of students (40.5%) and senior residents (41.2%) did not complete a single questionnaire. Nevertheless, virtually all first-year residents participated in the study, and the mean number of responses in this group was 5.88. The maximum number of responses from any one individual was 21 (or 5.10% of the total).

Relevant Diagnoses. Table 2 shows the relevant diagnoses that were made for the patients in this study. Seventy-three percent of patients were admitted with at least one disease that was "commonly" associated with an abnormality in serum electrolytes. In 238 cases, the diagnosis of this condition antedated the symptoms that brought the patient to the hospital. In 145 cases, new diagnoses were made shortly after the patient was admitted to the teaching service. However, despite the large number of patients at risk, electrolyte abnormalities were quite uncommon. Only 9.45% of patients were given the diagnosis of a new electrolyte disorder within 48 hours of admission, and most of these were simple abnormalities in the serum sodium and serum potassium. Nevertheless, it could be argued that these abnormalities led to the diagnosis of important diseases that otherwise would have been unsuspected. However, a review of the discharge summaries revealed only two diagnoses that were suspected solely on the basis of abnormal admission chemistries. One was a case of hyporeninemic hypoaldosteronism and the other was a case of SIADH.

Physicians' Motives. The house staff were willing to admit to many different reasons for ordering admission chemistries (Table 3). By far the most common reason was to confirm an abnormality suspected on the basis of the history and physical examination (59.0%). It was uncommon for a test to be ordered solely for the physician's benefit. In fact, at least one patient-related reason was given in 383 cases (or 93.0% of all admissions). Nevertheless, in 20.6% of cases, the house officer could identify at least one other person who wanted the initial studies. These "other" physicians were medical residents in 47% of admissions, private physicians in 57%, and full-time physicians in only 25%. All other personal reasons were uncommon.

First-year residents were less likely to use an admission test to confirm a suspected abnormality than medical students ($P = <0.02$). However, there were no differences between medical students, first-year residents, and senior residents in the other reasons given.

Types of Physician Response. An average of 5.3 serum chemistries were measured for each patient at the time of admission to the in-patient service. The results elicited a variety of written and therapeutic responses from the physicians involved in the patient's care.

Most of our house officers transcribed the initial test results (77.9% of cases) or simply noted the test (9.0%) by comments such as "electrolytes normal" or "electrolytes pending." It was far less common for any physician to assign a problem number to an electrolyte abnormality (10.2% of admissions), to write a new diagnosis (9.5%), or to explain the test results in progress notes (6.3%). Contingency analysis showed that there were significant differences in the frequency of transcription ($P < 0.001$), of other notations ($P = <0.005$), and of comments about repeat tests ($P < 0.001$) according to the physician's year of training. Medical students uniformly transcribed

TABLE 4

Correlation between Predictions and Outcomes

Probability of an abnormality	No. of responses	Clinical abnormalities No. (frequency)
75–100%	44	21 (47.7%)
50–74%	66	17 (25.8%)
25–49%	98	14 (14.3%)
0–24%	181	14 (7.7%)
No opinion	23	

test results into their progress notes. On the other hand, it was unusual for senior residents to acknowledge test results in any written manner.

There were no differences in the frequency of transcription or other notations between tests that were biochemically normal and those that were abnormal. Repeat values were more likely to be mentioned if the initial value was abnormal ($P < 0.001$), but this response also occurred for 10% of normal studies.

Test participants made therapeutic responses for 14.1% of patients. The most common abnormalities that required treatment were hypokalemia (6.1% of cases) and hyponatremia (5.3%). Other abnormalities were quite uncommon, and only 15 patients were treated for abnormalities in serum calcium, phosphorus, or magnesium. Overall, 45 patients had a biochemical abnormality that prompted a significant written response, and 58 had a biochemical abnormality that required treatment. The number of patients with either clinical abnormality was 73 (17.7% of all patients).

Prediction of Test Results. In 389 cases (94.4%), the admitting house officer was willing to estimate the probability that a significant abnormality would be found among the admission chemistries he or she ordered (Table 4), assigning one of four categories of risk.

Contingency analysis showed that there were significant differences in the frequency of abnormalities among the four groups ($P < 0.001$). However, for 3 of the 4 groups, the observed frequency fell outside of the expected range. Most of these errors were due to a tendency for our house staff to overestimate the risk in "high-risk" patients. This observation suggests that, while our house staff can recognize some differences in pretest risk, they are quite inaccurate in classifying patients into broad prognostic categories.

TABLE 5

Prediction of Individual Test Results

Study	No. of studies ordered	No. of abnormalities suspected	No. of abnormalities found	Accuracy of physician prediction*
Sodium	387	105	29	73.6%
Potassium	394	189	36	55.1%
Chloride	384	42	17	85.7%
Bicarbonate	384	100	21	73.2%
Calcium	254	91	8	65.0%
Phosphorus	224	40	11	82.6%
Magnesium	155	22	11	83.9%

* Accuracy = number of correct predictions/number of studies ordered.

As a result, the outcome of admission testing was unexpected in a large number of patients. Twenty-six percent of these outcomes were considered improbable (<50%) at the time the tests were ordered. Of those that were abnormal, 42.4% were considered improbable and were therefore unanticipated by the admitting house officer. Of those that were normal, 22.3% were unanticipated.

Table 5 shows the house staff predictions for the results of individual studies. In this case, we did not solicit graded responses from the admitting resident. Overall, our house staff were 73% accurate in predicting the results of the tests that they ordered. The most inaccurate predictions occurred for the tests that were most often thought to be abnormal.

Discussion

In order to contain laboratory costs, many institutions have developed programs to promote more effective use of the laboratory (1, 2). These programs have used a variety of interventions (3-9), and some have been quite effective. However, only one program (9) has managed to sustain a reduction in laboratory use over a period of years. In addition, others have noted a tendency for physicians to revert to their old habits of practice once the interventions are stopped (3, 7). These observations suggest that it can be quite difficult to change the way in which physicians use laboratory tests.

Many causes for excessive laboratory use have been identified (6, 12). However, few studies have examined the reasons for the use of a "superfluous" test on a case-by-case basis. Even fewer have correlated the outcome of each test with the physician's expectations to see if such behavior is positively reinforced. We therefore thought that it would be interesting to study the use of certain diagnostic tests at a community teaching hospital. We decided to study admission chemistries for a number of reasons: (a) electrolyte disturbances can complicate a variety of diseases seen on our medical service; (b) we could develop explicit criteria for a physician response to test abnormalities; (c) previous studies have shown that these tests are used excessively (13); (d) there is little evidence that admission chemistries have value as screening tests (10, 11); and finally (e) it has been suggested that these "small-ticket" items contribute excessively to laboratory costs (14).

We found that 73% of our patients were admitted with at least one disease that was "commonly" associated with an abnormality in serum electrolytes. In addition, we found that the measurement of serum chemistries is a very common practice among our house staff and that most of the residents are apparently motivated by the belief that these tests provide important information. Nevertheless, only 10% of our patients were given the diagnosis of an electrolyte disorder as a result of such testing, and less than 18% of these tests revealed a clinically significant abnormality. Since the yield of electrolyte testing is quite low, it is difficult to understand why these tests were used on almost every patient admitted to the teaching service.

We believe that part of the explanation can be obtained by comparing the expectations of our residents with the outcome of the tests. Our house staff were quite inaccurate in predicting the risk and the type of abnormality in serum chemistries on the basis of a history and physical examination alone. Most of the errors were due to a tendency for our house staff to overestimate the prevalence of clinical abnormalities. As a result, a substantial proportion of both normal and abnormal results were thought to be unlikely at the time that the tests were ordered. This observation suggests that the use of these studies could be reinforced by the high rate of unanticipated results.

We realize that our definition of a clinical abnormality was arbitrary. Nevertheless, we tried to observe certain principles in selecting our criteria. First of all, since we were interested in studying physician motives, we included test results that appeared to be important to the physician, even if they resulted in no treatment for the patient. Second, we chose criteria that seemed reasonable to the physicians who were most familiar with the house staff on the medical service. Finally, since we wanted to give the benefit of any doubt to the physician ordering the test, we chose criteria that were liberal instead of conservative. Nevertheless, our conclusions would have been the same if we had used a more restricted definition of "clinical significance." Since our house staff overestimated the prevalence of "clinical abnormalities," a strict definition of this term would have exaggerated the errors in their predictions.

We believe that the results of this study have important implications for future studies on laboratory cost containment. Many studies have used incentives in order to modify physician behavior (3, 4). These strategies seem to be based upon the premise that physician motives are somewhat deficient and that residents could be more selective if they "tried harder." However, our study shows that these assumptions are not necessarily true. Most of our house staff gave appropriate reasons for ordering laboratory tests, and most were inaccurate in predicting the outcome of specific tests on the basis of the history and physical examination. We are not convinced that the use of a test should be restricted in these circumstances. In addition, we found that one-fourth of normal test results were unanticipated. Future studies should give much more attention to the value of such results when they are obtained by inexperienced physicians. Finally, our study did not examine residents' opinions about the utility of different outcomes. It is possible that residents use laboratory tests because they perceive a high cost for a missed diagnosis (a false negative).

In summary, the measurement of serum chemistries seems to provide information that is otherwise unavailable to the admitting resident. We do not believe that such behavior should be discouraged unless there is some way to assure more accurate assessment of patient risk.

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Mount Sinai Hospital Medical Center of Chicago

The Olin-Sang Pavilion of Mount Sinai Hospital Medical Center. The center, a teaching associate of Rush-Presbyterian-St. Luke's Medical Center, is located ten minutes southwest of Chicago's loop.

History and Introduction

Mount Sinai Hospital Medical Center of Chicago is a 464-bed teaching hospital offering a full spectrum of health-care services including primary, secondary, and tertiary care. The physician staff is over 300. Founded as a 60-bed hospital in 1919 to serve the predominantly Jewish community that existed on the west side of the city, Mount Sinai now provides a whole range of services to its varied constituency.

Outpatients are treated through ambulatory care in department group practices on the campus and at three satellites in the city. The hospital assists physicians in opening practices throughout Chicago, particularly on the city's southwest side.

The hospital is now housed in four interconnected buildings: the new surgical building, the modern, 7-story Olin Sang Pavilion, the 12-story Frankel building, and the 11-story Kurtzon building.

Many of the hospital's programs are devoted to specialty care: intensive care for seriously ill newborns; diagnosis and treatment of cancer and blood disorders; a trauma center; new neurosurgical techniques for the relief of pain; in vitro fertilization; complete geriatric care; a homelike birthing suite for natural childbirth; family planning; home care; a comprehensive computerized diagnostic laboratory; an emergency-room rape-victim counseling program in which volunteers support women in crisis.

Currently the hospital trains more than 300 undergraduate and graduate physicians and nurses each year. As part of its affiliation with Rush-Presbyterian-St. Luke's Medical Center, Mount Sinai provides undergraduate medical training in medicine, surgery, obstetrics and gynecology, pediatrics, and psychiatry. Its continuing education programs have Category I accreditation by the American Medical Association.

Mount Sinai also has affiliations with Schwab Rehabilitation Center, the Liberman Geriatric Health Centre, and the Jewish Federation of Metropolitan Chicago.

The hospital conducts research programs on such medical problems as cancer, blood diseases, heart disease, stroke, pediatric illnesses, and care of premature infants. Members of its medical and scientific staffs have achieved international recognition.

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A History of Medical Research at Mount Sinai Hospital Medical Center of Chicago

MAXWELL P. WESTERMAN, M.D., AND STAN TYMOREK, B.A.

Mount Sinai Hospital was founded in 1919 by a group of Jewish men and women who lived on Chicago's West Side. These founders—including Morris Kurtzon, Mrs. Edwin Romberg, Rabbi Saul Silber, S. P. Platt, Mrs. Benjamin Shipman, Leopold Kling, and William Reiss—were concerned about the lack of adequate local hospital facilities for the approximately 600,000 West Side residents. Among these were more than 200,000 Jews, the majority of whom were Orthodox.

One of the main goals of the new hospital was to provide medical care for the area's Jews, including the many who had recently immigrated to America, in an environment that supported their culture, language, and religious practices. Mount Sinai was also meant to be a home for Jewish physicians, interns, and residents who had difficulty finding places on existing hospital staffs.

In addition to these services for the general population and the Jewish community, medical research was an integral part of the hospital from its inception. But the investigations conducted in the early part of this century differed greatly from today's research, which frequently involves the use of highly sophisticated instruments and methods. We have therefore divided the history of research at Mount Sinai into distinct periods reflecting the advances taking place in medical research.

The Early Years: 1920–1930

The research that was done at Mount Sinai during the twenties was an extension of very able physicians' clinical acumen and keen observations of patients.

Typical of these physicians was Isadore Trace, an internist who published early studies in cardiology and became one of the first electrocardiologists. He was a member of the medical staff from its formation in 1919 to his retirement in 1954. In a festschrift honoring Dr. Trace on his seventieth birthday in 1951, Israel Davidsohn, chairman of pathology at the time, wrote:

> His presentations of complicated clinical cases have been among the best I have ever heard. . . . He presents the clinical problem as he sees it, and sketches the difficulties and contradictions in bold relief. Then he works on each one of the difficult facts, resolves the contradictions, and fits them into the whole, one after another, until eventually the case becomes crystal clear and convincing. The logic of his reasoning, the systematic build-up, brick by brick, the fine subtle presentation, have made each of his contributions to the Friday conferences an unforgettable experience, and have no doubt contributed a lion's share to the popularity of the Mount Sinai conferences.

Among other outstanding clinicians and early clinical investigators in the department of medicine in these early years were Maurice Lewison, one of the first physicians to study and treat obesity as a disease; Ellis Freilich, who served on the medical staff from 1919 to 1971; and Harry Isaacs, another early electrocardiologist.

Neither clinical expertise nor writing was limited to one department; both were evident throughout the new hospital. In the department of surgery, for example, Alfred Strauss became widely known because of his innovative work and publication in gastrointestinal surgery. Among

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his talented colleagues during the 1920s were Victor Schrager in general surgery, Harry Richter, an early thyroid surgeon who was also a general and thoracic surgeon, and Charles Jacobs in orthopedic surgery.

In obstetrics and gynecology, two physicians stood out for their clinical and research work and medical writing: Aaron Kantor, a widely known gynecologist who developed the fish test, one of the first tests to determine pregnancy, and Abe Lash, M.D., Ph.D., who became well known for the use of the Lash operation for an incompetent internal os. Other active department physicians were Charles Newberger and Asher Goldfine.

Individual clinicians from other departments also laid the groundwork for the research of later years. James Lebensohn, a brilliant ophthalmologist, wrote over 160 articles on his speciality and translated a French ophthalmologic text. He also derived many useful optic formulas. Samuel Morowitz, a specialist in ear, nose, and throat problems, published extensively, including studies on the treatment of atrophic rhinitis. Pediatric neurologist Abe Levinson contributed pioneer work on the study of cerebrospinal fluid.

The Beginning of Basic Research: 1930–1945

During the 1930s, medical research at Sinai began moving to the laboratory, where for the first time patients' problems were further clarified and evaluated by physicians, biochemists, and physiologists and where new insights, procedures, and tests were being developed. This gradual transition to basic research continued until after World War II, when instrumentation and laboratory techniques became part of standard hospital practice.

Many of the physicians active in the twenties remained key staff members throughout the ensuing era. Among those who continued their work or became even more productive were Drs. Trace, Freilich, and Isaacs in medicine, Drs. Strauss, Richter, Schrager, and Jacobs in surgery, and Drs. Kantor and Lash in obstetrics and gynecology, as well as Drs. Lebensohn, Morowitz, and Levinson.

The beginning of the new era at Sinai was marked by the arrival of a physician who became known throughout the world for his work in immunohematology and immunopathology during his forty years on the hospital's medical staff. Israel Davidsohn, M.D., was born in Tarnopol, then part of the Austro-Hungarian Empire, to a family that valued the tradition of education. After acquiring a broad, general education, he began to study medicine at the University of Vienna in 1913. But at the outbreak of World War I he returned to Tarnopol, where he served as a volunteer medical assistant until 1917. After the war he went back to Vienna, receiving his degree in medicine in 1921. By this time he had also become a multilinguist. Fluent in Polish, Ukranian, and Yiddish—his childhood languages—he also mastered German, Hebrew, English, Russian, and French.

Determined to come to the United States, young Dr. Davidsohn accepted a position at Mount Sinai Hospital in Philadelphia (now Albert Einstein South), where he became the director of laboratories in 1929. He left this post when he was offered the position of chairman of pathology at Mount Sinai in Chicago.

Dr. Davidsohn began doing basic research before 1930, and eventually went on to write 160 papers and four books, including a classic text, *Clinical Diagnosis and Management in Laboratory Methods* (with Todd and Sanford). Among his papers were "Test for Infectious Mononucleosis," the major focus of his work from 1930 to 1945, and "Serodiagnosis of Malignant Tumors."

Another Mount Sinai researcher of this era whose papers received wide attention was dermatologist Samuel Zakon. During his forty-five years at the hospital, Dr. Zakon wrote 85 papers on clinical cases, research, and the history of medicine. One of the highlights of his work was "Effects of Androgen on the Sebaceous Glands of Human Skin," which he wrote with Hugo Rony, endocrinologist in the department of medicine. This paper recently received belated recognition when it was selected as one of the 12 most significant studies published in *The Archives of Dermatology* during its one hundred years of publication.

During this era, there were several outstanding pediatricians on the staff. Ben Gasul, an early pediatric cardiologist, studied and wrote extensively on heart disease in children, including a standard text, *Heart Disease in Children: Diagnosis and Treatment* (with Rene Arcilla and Maurice Lev). Three of his colleagues who were well known for the quality of their clinical work and their studies were Isidore M. Levin, who studied cystic fibrosis and lead poisoning, Philip Aires, and Maxwell Borovsky.

Another renowned member of the Davidsohn family, Gusta Davidsohn, came to Mount Sinai in 1935. Trained as a pediatrician in Poland and as a physiatrist under Dr. Krusen of the Mayo Clinic, one of the early giants in the field, Dr. Davidsohn was one of the first physiatrists in the

Chicago area. She became one of the early leaders in the field through her work as a clinician and teacher and her interests in clinical research.

Max Cohen joined the radiology department as chairman in the middle 1930s after an illustrious career as a diagnostician and researcher in Berlin. He was succeeded by Julian Arendt, whose writings included early, classic papers on hypertropic antral gastritis and on the radiologic aspects of infectious mononucleosis.

In the department of surgery, Leo Miller did early clinical studies on various orthopedic problems, and Harry Rolnick, a pioneer urologist in this prewar era, did several clinical studies and wrote a two-volume text, *The Practice of Urology: Male, Female, Pediatric*. Two physicians who were brothers, Earl and Major Greene, did considerable work in and published many articles on biliary-tract and gastrointestinal surgery.

New additions to the department of medicine who were active in clinical studies were Peter Gaberman and Donald Atlas, who wrote mainly on clinical topics, and Hugo Rony, M.D. Prior to coming to Mount Sinai, Dr. Rony had done some of the early work on insulin while on the staff of the Royal Hungarian Institute. His major research interests were in the biology of hair growth and fat metabolism and obesity; in addition to many published articles on these subjects, he wrote *Obesity and Leanness*.

In neurology and neuropathology, Ben Lichtenstein performed basic neuropathologic studies on tuberous sclerosis and neurofibromatosis.

With the beginning of World War II, research activities in the hospital slowed considerably and did not start again until the end of the war.

A Great Flowering: 1945–1970

The two decades after World War II were a time of enormous growth in research activities throughout the hospital. Researchers in virtually all departments performed significant work; highlights were the continuation of studies with far-reaching implications by Dr. Davidsohn and his colleagues in pathology, the addition of new, highly talented researchers in medicine, and an active cancer research program in the surgical department.

Pathology. During the 1950s, Dr. Davidsohn continued his earlier work on infectious mononucleosis and hemolytic anemia. He also published numerous papers on immunohematologic aspects of disease, including diseases of the lymph nodes. He collaborated with Kurt Stern on the identification of blood transfusion reactions and worked closely with Chang Ling Lee and others on studies of infectious mononucleosis and immune problems of the red cell and the lupus erythematosus cell.

In the mid 1960s Dr. Davidsohn began work on a test for the early detection of certain forms o cancer, the focus of his attention until his retirement in 1979. Stanley D. Kovarick collaborated with Dr. Davidsohn in this search. Albert I. Rubenstone, who joined the department of pathology in 1964 and is now chairman of the department has called this project "the culmination of Dr Davidsohn's work."

The design of the red-cell adherence test is based on the observation that natural antigens are formed in tissue cells and that as tissues become malignant, these antigens are lost. Dr. Davidsohn postulated, therefore, that he could test for malignancy by determining whether the cells of affected tissues contained antigens. Today, the test is widely used in a variety of applications. A most interesting use has been in determining the blood types of Egyptian mummies by testing their cell tissues. Egyptian physicians have also used the test clinically to study the relationship between schistosomiasis and bladder cancer, a prevalent disease in that country.

Another important clinical use of the test is in the management of carcinoma in situ of the urinary bladder. Since treatment of the disease is controversial and depends on invasion of the tumor, the test is done serially. If test results become positive, suggesting worsening of the tumor, then more aggressive treatment is indicated.

During the fifty years that Dr. Davidsohn worked at Mount Sinai, he received 13 major awards for his contributions to medicine and society. According to Dr. Rubenstone, Dr. Davidsohn derived his personal motto from a streetcleaner whom he met in his native city during World War I. In the midst of the political upheavals and combat around him, the streetcleaner could be seen quietly polishing the lamps of the town every day without fail. He liked to refer to his research as "polishing the lamp."

Dr. Kurt Stern joined the pathology department in 1945. He was born in Vienna and graduated from the University of Vienna Medical School in 1933. He completed internships in Vienna and was a research associate in the Institute of Biochemistry of the University of Vienna Medical School until coming to the United States in 1938. Dr. Stern spent several years in New York before starting at Sinai. During his years at Sinai he completed a number of studies on the immunologic approach to the treatment of cancer and laid the groundwork for the currently used method of preventing Rh hemolytic disease of newborns. He performed the first experiments showing that passively administered anti-Rh serum could interfere with primary Rh immunization. He found that if Rh-positive red cells were coated with anti-Rh serum and then injected into Rh-negative subjects, there might be no antibody response. He did not pursue these experiments, but the researchers who built on his work found that Rh immunization that would otherwise occur as a result of pregnancy could be suppressed by a timely injection of Rh antibody. Dr. Stern's experiments were of enormous importance for the later discoveries in prevention of hemolytic disease of the newborn.

During the 1960s, Dr. Chang Ling Lee joined Israel Davidsohn in studies of experimental hemolytic anemia. Dr. Lee also worked with Dr. Davidsohn on developing the differential test for infectious mononucleosis which Dr. Davidsohn had been working on since 1935. Together the pathologists improved upon the standard test for this disease by using the red cells of horses, which proved to be much more sensitive than the commonly used sheep cells and also markedly reduced the time it took to complete the test, now known as the mononucleosis spot test.

Dr. Lee also studied the lupus erythematosus cell, trying to simplify the procedure for determining whether there is an antigen-antibody reaction in the cell inclusion. Dr. Lee devised a method of obtaining a smear of white blood cells and serum by which he could detect these reactions with greater sensitivity.

In his research in blood banking, Dr. Lee developed a more efficient way of crossmatching blood and later went on to examine and develop systems for paternity testing.

Other researchers were active in pathology during this period. Harry Weisberg joined the department in 1949 as the head of the division of clinical chemistry and biochemistry. Dr. Weisberg's main areas of investigation were water and electrolyte balance, diseases of lipid metabolism, and parenteral fluid therapy in adults.

Spyridon G. A. Alivisatos, M.D., Ph.D., succeeded Dr. Weisberg as head of biochemistry research in 1955. In over 200 publications in chemistry and biochemistry, Dr. Alivisatos has described the mechanism of action of biogenic amines, the metabolism of the brain, and the physiological role of cholesterol and was the first to describe lactic dehydrogenase in human serum.

Milton Goldin, Ph.D., joined the pathology staff in 1949 as a bacteriologist and is currently the head of that division. In his early years at Sinai, Dr. Goldin collaborated with Dr. Israel Davidsohn and Dr. Stern on several studies. He has continued to publish on bacterial growth, resistance, and synergism, and has also described useful methods for hospital bacteriologic laboratories.

During the mid 1950s Henry Rappaport, a member of the pathology department, published widely and completed a number of significant studies on lymphomas.

In 1960, Douglas Huestis, M.D., came to the department as a clinical pathologist and director of the blood center. During his nine years at Mount Sinai, Dr. Huestis performed a number of studies on various aspects of blood transfusions. In 1969, he and research associate Shirley Bush published *Practical Blood Transfusions,* a widely used text in the field.

Raoul Fresco, M.D., Ph.D., who joined the pathology staff in 1964, collaborated with Douglas Huestis and Shirley Bush on developing a simple method of preparing "coated" red cells for use as a control in antiglobulin testing. While at Mount Sinai he published several studies on such topics as ultrastructural investigations of blood cells and virus-like particles and applications of the electron microscope to diagnostic pathology.

Eva Krompotic, M.D., was a researcher in the cytogenetics laboratory from 1964 to 1973. She published several studies on cytogenetics, including work on the clonal evolution of Di Guglielmo's syndrome and chromosomal aberrations in chronic granulocytic leukemia during blast transformation.

Albert Rubenstone, M.D., became chairman of pathology in 1965. Dr. Rubenstone's research interests have been extensive, ranging from the diagnosis and origin of malignant lymphomas and leukemias to elastosis in breast lesions, from senile cardiac amyloidosis to the evaluation of red-cell adherence testing in bladder tumors.

In addition, many persons participated in the research activities of the department at different levels and for various periods. Claude Biava, Ph.D., worked primarily on electron microscopic aspects of the departmental research studies. Takashi Makinodan, Ph.D., who has since been very involved in radiation immunology, the mechanism of antibody formation, and aging of the immune system, was a member of the department in the early 1950's.

Medicine. A renowned researcher joined the department of medicine in 1950. Aldo Luisada received his medical training at the Royal University of Florence Medical School and later obtained the Italian equivalent of board certification in clinical pathology and in internal medicine. Dr. Luisada also completed postgraduate training in cardiology under Professor Vaquez in Paris and in pharmacology under Professor Loewi, a Nobel Prize winner, at Graz and Professor E. P. Pick in Vienna. When he was dismissed from his position as professor and chairman in the department of medicine at the Royal Universities of Sassari in Italy because of the government's anti-Semitic laws in 1939, Dr. Paul White, the eminent Boston cardiologist, helped him immigrate to the United States.

After holding several clinical positions in the Boston area during the 1940s, Dr. Luisada came to Chicago and set up an experimental and clinical laboratory in an annex of Mount Sinai. His initial animal experiments focused on the mechanism and treatment of acute pulmonary edema and the transplantation of the heart in dogs. These early studies on the treatment of pulmonary edema included the use of defoaming agents. His early clinical studies at Sinai involved the study of heart patients by electrokymography and phonocardiography.

In 1953, a cardiology laboratory was established in the Frankel Building, and in 1955 a cardiac catheterization laboratory was added. Dr. Luisada and colleagues performed various studies on the catheterization of the right side of the heart. In 1957, the Sinai researchers became one of the early groups of cardiologists to accomplish catheterization of the left side of the heart. Dr. Luisada and C. D. Liu, M.D., also routinely recorded sound tracings from inside the heart.

Dr. Luisada has written extensively on his work, including five books and eleven monographs. Since leaving Mount Sinai ten years ago, his research interests have been primarily related to studies of heart sounds. In addition to his clinical and research activities, Dr. Luisada was a founder of the Laennec Society of the American Heart Association.

In 1957, Hyman Zimmerman became the chairman of the department of medicine. He had received his medical training at Stanford University School of Medicine and had been involved in extensive studies of metabolism of the liver, liver toxicity, and other aspects of liver disease. During his eight years at Mount Sinai, Dr. Zimmerman began more in-depth studies of the mechanisms of liver toxicity. At that time, the clinical usefulness of determining enzyme serum levels had just been established. Dr. Zimmerman studied the factors that influence the levels of blood enzymes and the enzyme levels that physicians could expect to find in the blood of patients with various types of diseases.

This was a very productive time in the department of medicine. Dr. Zimmerman considerably expanded the research, clinical, and teaching aspects of the department. Joining him in the studies on liver disease were Michael West, Roy Korn, and Leonard Seif. In the endocrinology and nuclear medicine units, Leigh Rosenblum and Maurice Schwartz were studying various endocrine disorders. Also during this period, Gordon Snider performed substantial work on many aspects of lung disease, including diagnosis and management. Lung Yam, a trainee in the department at this time, later went on to original studies on cytochemical identification of the cells of hairy-cell leukemia and on monocytes and granulocytes.

Other members of the department were also engaged in research. In the late forties and early fifties, Steven Schwartz made important hematologic research contributions, while Fred Steigmann was doing active research in gastroenterology. About the same time, Arnold Black was examining various aspects of arthritis and Abe Aaronson was doing studies on allergy. Later, Morris Kaplan, a clinical research allergist, joined the staff. In the kidney program, Philip Freedman was following up on immunologic studies on the kidney in systemic lupus erythematosus.

Surgery. During the 1950s, Mount Sinai was one of the early laboratories investigating chemical carcinogens. Organized under the department of surgery, the chemical carcinogenesis program was directed by Philippe Shubik, M.D. In 1950, Dr. Shubik established a cancer research laboratory in the new Frankel building and recruited a number of highly qualified investigators. Included among the researchers who worked with him in the 1950s were Umberto Saffiotti M.D., Willie Lijinsky, Ph.D., Renato Baserga, M.D., Alex Ritchie, M.D., Benedict Terracini M.D., Lorenzo Tomatis, M.D., Regina Schoenthal, M.D., Guiseppi Pietra, M.D., Herber Hadler, M.D., Guiseppe Della Porta, M.D., and Leonard Kolb, M.D.

Among the many accomplishments of the grou during this period were numerous studies on th induction of skin cancer by Dr. Ritchie, Dr. Baserga, and Dr. Saffiotti. Dr. Saffiotti and Dr. Rit chie demonstrated the ability of an orally administered carcinogen to act systematically as an initiator of skin carcinogenesis. These studies were extended by other members of the group, which consisted of Drs. Della Porta, Pietra, Scortecci, Terracini, and Tomatis. Dr. Lijinsky evaluated the chemical structure of the carcinogens while Dr. Schoenthal evaluated the carcinogenic effects of environmental combustion products. Leonard Kolb, who became a member of the department of surgery in 1938 and is currently a senior attending physician at Mount Sinai, joined Dr. Shubik and Dr. Della Porta in experiments on the induction of tracheobronchial carcinoma in the hamster.

As a member of the department of surgery during the 1950s, William Schumer, M.D., M.S., wrote several articles on surgical management and technique for operations, particularly for gastrointestinal diseases. He went on to study and publish extensively on the treatment of burns. Later Dr. Schumer did significant work on shock and microcirculation. Tapas Das Gupta, M.D., who did his surgical training at Sinai during this period, has made major experimental and clinical contributions in cancer diagnosis, spread, and treatment and in physiologic studies of the lung and gastrointestinal tracts.

Richard Dewall, chairman of surgery from 1963 to 1967, was a pioneer in the development and use of the bubble oxygenator, an important advancement in the support systems needed for open-heart surgery. Mohan Airan, M.D., then a surgical resident and now chief of general surgery at Mount Sinai, was associated with Dr. Dewall in the use of the newly developed double bubble oxygenator with the first 10 patients. Also at this time, Hassan Najafi was engaged very actively in cardiovascular and thoracic surgical research. Dr. Najafi has published many innovative and significant studies on cardiovascular surgery. Leonard Kolb collaborated with members of Dr. Shubik's group on studies describing the experimental induction of bronchogenic cancer, which allows for closer examination of the pathogenesis of human lung cancer. Jules Whitehill, who did very early studies on the electromagnetic measurement of blood flow and later work on a semiautomatic device for anastomosis, was an attending surgeon and chairman of surgery during the latter part of the 1960s.

Thomas Baffes became chairman of the department in 1968. As a colleague of Dr. Willis Potts at Children's Memorial Hospital in Chicago, Dr. Baffes had been involved in the initial development of various types of congenital heart surgery as well as in studies of the transposition of the aorta and pulmonary artery. He has published papers on several aspects of surgical care of congenital heart disease.

During this period, members of the surgical subspecialties were also active. Dr. Harold Feinhandler, for one, studied the effects of vibration on the eye as part of the aerospace program studies.

Psychiatry. Harry H. Garner, the chairman of psychiatry since 1949, performed most of his research during the 1960s. His studies were primarily focused on the confrontation technique in psychotherapy and psychosomatic management of the patient with malignancy. In addition to numerous papers, Dr. Garner wrote two books on these subjects.

LeRoy Levitt came to the psychiatry department in the same year as Dr. Garner, in the position of attending psychiatrist and director of the outpatient psychiatric clinic. Dr. Levitt, who is now chairman of the department of psychiatry and behavioral sciences, has studied psychiatric aspects of aging and has collaborated with Dr. Alivisatos on studies of serotonin activity in the central nervous system.

Anesthesiology. Ruth Weyl, M.D., was the chairman of the department of anesthesiology from 1949 through 1965. She collaborated with Dr. Luisada in cardiology on research projects and published the first paper on the use of methohexital sodium in anesthesiology. She was succeeded by Henri Havdala, M.D., who with Bruce Diamond, Ph.D., extensively studied many pharmacologic and metabolic activities in the central nervous system.

Radiology and Radiation Therapy. The first radiation therapist, Erwin Japha, M.D., was appointed and served as the director of this unit from 1957 to 1971. Dr. Japha's research focused on the treatment of retinal glioma, cancer of the larynx, and carcinoma of the female breast. George Greenfield, M.D., current chairman of the department of radiology, has been interested in and has published studies on radiologic aspects of bone disease. Stefano Stefani, M.D., director of radiation therapy, has pursued wide-ranging interests in the immunologic aspects of radiation.

Pediatrics. Aaron Grossman became the chairman of pediatrics in 1964. His research interests were in the management of acute and chronic glomerulonephritis. Paul Wong, who was director of the premature and newborn nursery and of the Infant's Aid perinatal research laboratories, studied many congenital metabolic defects, including maple-syrup urine disease and homocysteinuria, as well as enzyme changes in autosomal trisomy syndromes, the effect of maternal amino acid imbalance on the fetal brain, and other inborn errors of metabolism.

Obstetrics and Gynecology. During the late 1940s in obstetrics and gynecology, Charles Field, Sam Turner, Al Weiner, and Maxwell Wacker followed the clinical research tradition of their predecessors. Dr. Field's studies related to the significance of the lower uterine segment in labor. Dr. Turner was interested in antibiotic prophylaxis for vaginal surgery and systemic lupus erythematosus during pregnancy.

Robert Pildes, who joined the department in the late 1950s, performed a number of studies on the anovulatory ovary. Toward the end of the 1960s, Robert Stepto, M.D., Ph.D., became chairman of the department. Dr. Stepto has been interested in obstetric and gynecologic endocrinology and did early studies on the role of testosterone in tissue synthesis.

Summary

From astute early clinical observations to breakthroughs in pathology to pioneering programs in carcinogenesis and cardiology, the tradition of research at Mount Sinai Hospital Medical Center of Chicago has been rich and diversified. The medical staff hopes to maintain the spirit and traditions of these researchers for many years to come.

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The Practice of Tubal Sterilization: Review of a Departmental Practice Pattern

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Abstract

Within the framework of departmental peer review and quality control of care, a short-term prospective study of 75 consecutive tubal sterilization patients was performed to determine the departmental practice pattern in respect to tubal sterilization. This study revealed important socioeconomic profiles for various patient groups and led to acceptable departmental recommendations for change in certain clinical practices. It is concluded that short-term prospective evaluations of departmental practice patterns may be an effective and easily achievable method of investigating and modifying departmental practices in a way that is generally acceptable to the different physician groups within a department.

Tubal sterilization has not only achieved recognition as a preferred means of birth control but also represents a significant part of the surgical experience in every gynecological unit (1). Although individual approaches to tubal sterilization have been extensively investigated (2, 3), only limited information is available on the pattern of practice in various departments.

The reorganization of our department, instigated by the establishment of a full-time faculty representing all board-recognized subspecialties, led to an investigation of various departmental practice patterns. This was done in an attempt to reorganize departmental practice patterns in accord with specific departmental requirements without opposition from departmental "old-timers." Because of the popularity of the vaginal approach to tubal ligation among many voluntary staff members, the tubal sterilization practice pattern was chosen as one of the first targets for such an investigative effort. Some members of the faculty believed that, in view of earlier published experience (4–7), the vaginal approach carries a higher morbidity and failure rate and is therefore only rarely indicated. Because this contention was disputed by some staff members, it was agreed that a four-month prospective study which would allow unbiased evaluation of departmental practice patterns and indicate some short-term results would be performed. The findings of this study are presented in an attempt to demonstrate the validity of such an approach within the framework of departmental peer review.

Materials and Methods

We investigated prospectively over a four-month period the gynecologic tubal sterilization pattern for 75 consecutive patients entering the department. Postpartum tubal ligations were not included in this study. The data were accumulated by the chief resident of the Gynecology service and included all patients from both the private and the teaching service.

Statistical analysis was performed by standard *t*-test and chi-square analysis. The significance level chosen was $p = >0.05$.

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TABLE 1

Profile of Population of 75 Patients (39 private insurance, 36 Public Aid)

	Mean	Range	p value
Age (years)			
All patients	28.4	21–40	
Insured Patients:			
white	23.4	21–38	<0.005†
nonwhite	33.3	21–40	
Public Aid Patients*	24.4	21–40	<0.005‡
Gravidy			
All patients	3.6	1–9	
Insured Patients			
white	3.2	1–7	
nonwhite	4.0	1–9	
Public Aid Patients*	3.3	2–7	
Weight (Lbs)			
All Patients	141.0		
Insured Patients	134.6		<0.05
Public Aid Patients	152.3		

* Separation into white and nonwhite statistically not feasible due to smaller number of white patients in this group.

† $p < 0.005$ (insured white and nonwhite).

‡ $p < 0.005$ (insured nonwhite and all Public Aid).

TABLE 2

Method of Sterilization and Related Parameters

	No.	(%)	Mean Weight	Mean Days in Hospital†	Surgical Complications n (%)
Open/closed laparoscopy	45	(60)	185.9*	2.1	2 (5.7)
Vaginal tubal ligation	22	(29.3)	102.6*	1.9	3 (13.6)
Abdominal tubal ligation	8	(10.6)	137.7*	3.0	0 —
TOTAL POPULATION	75	(100)		2.7	5 (6.7)

* Statistically significantly different from each other at $p < 0.005$.

† Privately insured patients only; Illinois state requires Public Aid patients to undergo ambulatory tubal sterilization unless medically contraindicated.

Results

Among the 75 patients in the study group, 39 were privately insured and 36 were supported by Public Aid. The mean age was 28.4 years. Among insured patients, nonwhite patients were significantly older at time of sterilization ($p < 0.005$) than either their white counterparts or the combined white and nonwhite Public Aid group. (The latter group could not be statistically separated by race because of the very small number of white patients in the group.) No statistically significant differences in gravidy were noted among the subgroups, although insured nonwhite patients seemed to have a somewhat higher gravidy than white insured and all Public Aid patients. Thus, surprisingly, white insured and Public Aid tubal sterilization patients had a similar patient profile which differed from that of the nonwhite insured patient (see Table 1).

While insured patients in toto had a significantly lower weight than Public Aid patients ($p < 0.05$), there were no statistically significant differences between subgroups.

In accordance with generally accepted practice patterns (8), most tubal sterilizations were performed by laparoscope (60%), followed (surprisingly) by vaginal tubal ligations (29.3%) and, last, abdominal tubal ligations (10.6%); see Table 2.

Interestingly, the laparoscopic approach was primarily chosen for the highest weight group (mean weight lbs 185.9), the abdominal approach primarily for the median weight group (lbs 137.7), and vaginal tubal ligations primarily for the lowest weight group (lbs 102.6). The differences in weight between these three subgroups were statistically highly significant ($p < 0.005$).

Length of hospitalization could be evaluated for privately insured patients only, because Illinois Public Aid regulations require tubal sterilizations to be performed on an ambulatory basis unless a medical contraindication exists to such an approach.

Abdominal tubal ligations required the longest hospitalization (3 days), followed by laparoscopy (2.1 days) and vaginal tubal ligation (1.9 days).

No significant operative morbidity was encountered in this series. Nevertheless, short-term evaluation of the three surgical approaches to tubal sterilization revealed that surgical complications were highest (13.6%) in conjunction with the vaginal approach, followed by laparoscopy (5.7%); the abdominal approach had no complications at all. Complications in association with the surgery were basically restricted to failure of tubal interruption by chosen surgical approach. All failed vaginal and laparoscopic approaches were later successfully completed by abdominal tubal ligation.

Minor complaints in association with the various surgical approaches showed certain trends but did not reach statistical significance. Thus, shoulder and back pain were more prevalent with laparoscopy; abdominal pain was more prevalent with both abdominal tubal ligation and vaginal ligation.

It is interesting to note that the privately insured patients, who were all admitted to the hospital for their surgical procedures, received various analgesic drugs postoperatively, most including parenteral narcotics. Contrary to that, ambulatory Public Aid patients were managed satisfactorily with oral analgesics of 30–60 mg codeine only.

Discussion

The review of our departmental tubal sterilization practice pattern revealed a surprisingly large complement of data concerning both socioeconomic and clinical aspects of the practice of medicine.

Many of the characteristics of the study population were a surprise, particularly the clear difference in the profile of nonwhite patients who were privately insured and those who were Public Aid patients. The similarity between the profile of the Public Aid and the privately insured white population deserves further investigation. A recent report (9) has suggested that sterilization patterns in white and nonwhite populations have become similar. However, a difference within nonwhite groups depending on socioeconomic status has not, to our knowledge, been reported. The stronger desire for sterilization in Public Aid nonwhite recipients may be due to their poorer economic situation. It is, however, important to note that in these patients increased pregnancy rates do not seem to represent a primary reason for the desire for sterilization. This seems the case because insured nonwhite patients had a higher gravidy (4.0) than Public Aid patients (3.3). The latter group had, in fact, a gravidy almost identical to the insured white patient population. Undoubtedly, socioeconomic factors do play a major role in the decision for sterilization in women. Further clarification of these aspects are needed for an appropriate counseling process.

Clinically this research also resulted in interesting recognitions. The distribution of surgical approaches to tubal sterilization in our department seems to reflect national trends (8). The introduction of laparoscopy has made the various modifications of this particular surgical approach undoubtedly the most popular one (2, 8, 10). The incidence of vaginal tubal ligation may exceed that in many departments but may reflect a return of vaginal tubal ligations into the clinical practice pattern in various areas of the country (3, 6).

This study was not performed to compare long-range outcome between the different surgical approaches. Its purpose was only to investigate the departmental practice pattern and related short-term complications. Nevertheless, the study did reveal that of the three methods used, the vaginal approach to tubal ligation clearly carried the highest surgical failure rate. Whether this observation supports the contention widely supported by reports in the literature (7) that vaginal tubal ligations are only rarely indicated, or whether vaginal ligation is returning in clinical practice, remain to be established. It was most surprising, however, to note that vaginal tubal ligations were primarily performed on the low-weight patient while laparoscopies were the procedure of choice for the high-weight group. This observation within our departmental practice pattern contradicted generally accepted practice patterns and is contrary to common sense. Undoubtedly, laparoscopic tubal ligations are most difficult in obese patients, while the vaginal approach has been particularly recommended for the obese patient. The results related to weight suggest improper patient selection for the various surgical approaches and have already resulted in departmental recommendations for change.

Such recommendations were also issued concerning ambulatory surgical approaches. All Public Aid surgery had to be performed on an ambulatory basis in order to conform with Illinois state requirements. Among 36 procedures performed in such a setting, only one patient needed short-term hospitalization for observation. The use of medication was much higher in the hospitalized privately insured patient population and included the extensive use of parenteral narcotics. Thus ambulatory tubal ligation not only represents a medically safe surgical approach but seems also to decrease drug use and is significantly more cost efficient. Length of hospitalization for tubal sterilization has been constantly decreasing (11). It has been clearly stated that "even greater economical savings could be achieved if sterilization techniques requiring shorter hospital stays are to be more widely used" (11).

In summary, the study outlined here not only provided highly relevant socioeconomic and clinical data concerning our tubal sterilization population, but also resulted in the recognition and correction of certain aberrant departmental practice patterns. This study thus allowed us to reach departmental recommendations that were indisputable by departmental members because of specificity for the departmental situation.

We conclude that short-term prospective reviews of departmental practice patterns represent a highly effective method of guaranteeing quality control of care, peer review, and generally acceptable departmental recommendations for practice pattern changes within a medical department.

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A Hospital's Response to the Increasing Incidence of Child Abuse and Neglect in an Inner-City Population

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The reporting of child abuse and neglect to official state agencies has increased at an alarming rate following the implementation of obligatory reporting laws by each state. In 1980, over 788,000 reports were filed (1), and each of these reports involved the suspected maltreatment of an average of 1.5 children, resulting in a projection of suspected maltreatment of over 1,500,000 children per year (2). Moreover, since 1980, the number of reports has increased approximately 12% per year (3).

In 1977, Mount Sinai Hospital Medical Center in Chicago, Ill., initiated a formal longitudinal prospective study designed to accomplish three major objectives:

1. Quantify the incidence and define the problem of abuse and neglect in the population served by the Medical Center.
2. Determine whether the apparent increase in the incidence of reports to the Illinois Department of Children and Family Services (IDCFS), the state social service agency responsible for protecting children identified under the state reporting act, was due to an increasing awareness of the problem or to an actual increment in the number of abuse and neglect cases in the population.
3. Describe the topology, demography, trends, and confounding variables observed in reporting childhood maltreatment.

Methods

Patient data was gathered and entered into a file-and-retrieval program written for an Apple II computer located in the Pediatric Department offices. Data was collected daily, collated and trended monthly. The identification and subsequent control of variables was accomplished in four phases, each separated by a period of four to six months to allow for stabilization of reporting practices.

Phase I. In late 1977, a formal system to collect data on all suspected child abuse and neglect patients at Mount Sinai Hospital Medical Center, Chicago, Ill., was developed. Baseline information was obtained on the parents' marital status and age, identification and age of the primary caretaker(s), address and zip code, relationship to the child of the person bringing the patient to the hospital, immunization status of the child, number of siblings, number of previous hospital admissions, number of prior reports filed against the family, the type of injury incurred, and whether there was a delay in seeking medical attention, as well as many other significant factors.

Phase II. In 1978, we implemented a systematic approach to aid in the recognition of child abuse and neglect and understanding of both the substance and procedural mechanisms of the state reporting law. Phase II objectives were addressed in the following manner:

- An intensive educational program was initiated within the Department of Pediatrics targeting physicians (attending staff and house officers), nurses, and social workers.
- Case discussions, seminars, "morning reports," and multidisciplinary conferences were conducted.

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- Quality assurance projects, including chart audits using a medical model, were initiated. (All children suffering from "traumatic" events were included.)
- Individual procedures were delineated for cases of suspected abuse, neglect, or sexual molestation.
- Departmental policies were established, including mandatory admission to the hospital of all patients in whom the diagnosis of abuse or neglect was suspected; review of all emergency-room and ambulatory Pediatric medical records by the chief resident, department chairman, or research associate; inclusion of photographs or drawings of injuries in the hospital record; and consultation with the departments of Psychiatry, Obstetrics and Gynecology, Occupational/Physical Therapy, and Recreational Therapy in appropriate cases.
- "Pocket card" abuse and neglect protocols (see below) were designed and distributed to medical, nursing, social service, occupational, physical, and recreational therapy personnel.

Protocol for the Management of Suspected Child Abuse and Neglect

A. Report the case by telephone to the mandated state agency. This report is to be made by the examining physician, nurse, or other health professional (as per the state law). Record the name of the individual to whom the report is given as well as the date and time.
B. Complete a written report as soon as possible.
C. Admit the child if there is any question about the safety of his/her home environment, even if there does not appear to be a clear "medical" indication for hospitalization of the child.
D. Admission Orders:
   1. Social Service consultation.
   2. Psychiatric consultation: Mandatory in cases of sexual/physical abuse; otherwise, optional unless the child is exhibiting behavior of concern to the staff.
   3. Occupational Therapy consultation: Initially for developmental screening as a baseline in young children and repeated during the hospital course for comparison.
   4. Skeletal Survey: Mandatory for children suffering from physical abuse or if any history of prior trauma is elicited.
   5. Obstetric and Gynecology consultation: Mandatory in cases of sexual molestation or genital trauma in female children (see sexual molestation protocol).
      a. VDRL serology.
      b. Gonococcal cultures of the vaginal/penile, rectal, and oral areas.
      c. Chlamydial cultures (as per gonococcal cultures).
   6. Photographs should be taken, as soon as possible, of any manifestations of physical injury (burns, lacerations, bruises, old scars), as well as any manifestations of failure to thrive, neglect, malnourishment, or severe dehydration. While awaiting photographic documentation, representative drawings should be placed in the chart along with a pertinent narrative on the initial history and physical examination form.
   7. Recreational Therapy consultation: To obtain a practical assessment of the child's behavior, as well as to incorporate all potential modalities available as diagnostic aids.
   8. Samples of urine, emesis, and blood should be sent for analysis in cases of known or suspected ingestions.
      a. Screening for the specific drug (if known).
      b. General drug screening (if unknown).
   9. In cases of Failure to Thrive (FTT):
      a. The weight, height, and head circumference at the time of admission should be plotted on appropriate growth charts and included in the medical record.
      b. The birth weight, as well as pertinent perinatal information, should be recorded.
      c. The name of any hospital/clinic/physician providing prior medical care should be noted.
      d. Accurate daily weights should be charted at a predetermined time and utilizing the same scale.
      e. Dietary consultation is often of pivotal importance.

Protocol for the Management of Sexually Abused Children

1. The patient and accompanying family members (caretakers) should be escorted rapidly to a private room for the ensuing interview and physical examination.
2. The senior Pediatric resident should see all cases and assume primary responsibility for their care. An attending staff pediatrician should be notified as soon as possible.
3. The resident should be aided by Social Service and should obtain consultation from Gynecology. Psychiatry consultation may, in many cases, be needed acutely.
4. The history should be obtained from the patient alone (if possible) and then from both the patient and the guardian (conjointly), using quotations when available and supplemented by the child's drawings. (The sequence of interviews will vary with the presentation.)
5. The initial physical examination should be brief, noting any abnormalities, especially about the genital area. This examination should, in most cases, be performed with the help of a gynecologist. Appropriate cultures (trimucosal) should be taken in all suspect sexual molestation cases along with pertinent serologies. Cultures for *Chlamydia* and wet mounts for *Trichomonas* should be performed as indicated. If genital abnormalities are noted, a more complete exam should be performed, ranging from a simple aspiration of the vaginal contents with an eye dropper through a complete pelvic exam using the "rape kit."
6. The Pediatric resident and social worker should discuss the findings with the victim and the caretakers in a manner that is meaningful to both (avoiding unnecessary confrontations).
7. Adolescents should be counseled about the alternatives to a potential pregnancy as well as the risks of possible venereal disease. Treatment should be case-specific and individualized. (Not all cases of child molestation will require antibiotics.)
8. The caretakers should be given advice regarding possible future guidance and therapy of various personality disturbances that may be forthcoming, i.e., anxiety manifestations, phobias, sleep difficulties, regression.
9. A police report will often be required and a report to the mandated state agency is a must!

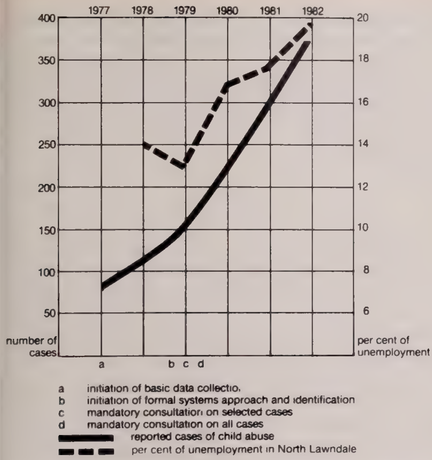

FIG. Rates of child abuse reported by Mount Sinai Hospital Medical Center, Chicago, Ill., compared to unemployment in North Lawndale, Chicago. From *Caring*, Vol. 8, No. 4, Winter 1982/83. National Committee for the Prevention of Child Abuse. Reproduced with permission.

Phase III and IV. Selective control of reporting sources (Phase III) was accomplished by requiring mandatory consultation with the Pediatric service on patients less than 17 years of age whose "primary illness" required that they be housed on the orthopedic or neurosurgical services. Subsequently, because of obvious changes in the number of reports generated, the by-laws of the Medical Center were altered to require Pediatric consultation on all patients less than 17 years of age regardless of the admitting physician or "service location" in the hospital (Phase IV).

Results

In the years 1976 and 1977, prior to the institution of the formal data-collection program, approximately 80 cases of child abuse or neglect were reported by our Child Advocacy Team to the Illinois Department of Children and Family Services. After initiation of the education component (Phase II) in 1978, there was a brisk rise in the number of case reports, resulting in a 41% increase over the previous year (Fig.). This trend continued, although it was less dramatic, over the next two years of data collection (the phase-in period). Ongoing tracking after completion of Phase IV has revealed a continuous and unanticipated increase in the number of cases reported of 35% (1980) and 40% (1981). When this trend is plotted against unemployment in the surrounding community, there appears to be a noteworthy correlation (see Fig.).

Discussion

Mount Sinai Hospital Medical Center is a 460-bed inner-city teaching institution providing primary, secondary, and some tertiary care to the contiguous Chicago communities of North and South Lawndale as well as serving a referral population from more distant areas. Many residents of North and South Lawndale are impoverished, living significantly below the national poverty level (4). Unemployment is rampant and has increased dramatically over the study period (14% unemployment at the onset of the project, and 19.8% by April 1982; the City of Chicago 1982 unemployment rate was 10.7%). The density of the communities is extreme, with a population of more than 200,000 residing in an area of less than 3.5 square miles (5). These communities are also unusual because of the inordinate number of single-parent households and teenage parents (6).

In order to pursue the objectives of the study, it was necessary to identify, segregate, and minimize confounding variables. At the completion of Phase I, certain variables were identified and isolated; they were then dealt with sequentially in subsequent phases. Data were collected, collated, and assessed in an ongoing manner.

Phase II involved the implementation of a systematic approach to stabilizing the variables so that actual trends could be more confidently appreciated. Prior to this, tremendous variation was known to exist in certain areas, including:

- The level of knowledge of child abuse and neglect (diagnosis, management, disposition) within the Pediatric Department and among "non-Pediatric" members of the medical and hospital services staff.
- The application of abuse-and-neglect diagnostic criteria to children seen in the emergency service or admitted to the hospital.
- The management techniques used when abuse or neglect was suspected.
- The communication of information when the same child subsequently came to the hospital again for questionable injuries or conditions.
- The level of reliability of communication between staff members.

Thus, Phase II began with the education of members of the Department of Pediatrics by developing and maintaining a consistent level of diagnostic acumen through ongoing inservice programs using various educational modalities (grand rounds, case discussions, lectures, multidisciplinary conferences, and daily morning-report conferences). Inpatient, emergency-room, and outpatient records were reviewed regularly to control for adequate application of diagnostic criteria. Repetition and reinforcement were provided to compensate for the tendency to minimize, deny, or mitigate relevant assessments and concerns. Since our Pediatric residents rotate at two other Chicago-area hospitals for significant periods of time, a vigorous effort was made to educate incoming house staff through problem-based learning techniques, independent study, and dramatic role-playing simulations of encounters with patients and parents. Using these methods, we were able to provide experience and teaching in both broad and specific areas related to childhood maltreatment in a short period of time.

An important factor in the education of our transitory house staff was the Child Advocacy Team (CAT). Our CAT is a mandated hospital-based multidisciplinary team consisting of representatives from the departments of Pediatrics, Nursing (Pediatric and Emergency Room), Administration, Occupational Therapy, Psychiatry, Recreational Therapy, and Social Service and a representative from the Illinois Department of Children and Family Services. The team formally and informally participates in the assessment and management of all patients with a diagnosis of suspected abuse or neglect.

Phase III of our project was addressed by enhancing access to the patient by an expert Pediatric staff, rather than trying to directly raise the level of knowledge of non-Pediatric personnel. Mandatory Pediatric medical consultation on children who were orthopedic and neurosurgical patients was initiated. A brisk rise in reporting cases of abuse and neglect was immediately apparent, and was most likely due to the recognition of preexisting problems in patients for whom a diagnosis of abuse or neglect had not previously been entertained and who had not been "available" to the Pediatric medical staff.

With this information at hand, the hospital medical staff bylaws were changed so that the Pediatric medical staff was able to consult on all patients under the age of 17 years, regardless of the primary service to which the patient was assigned (Phase IV). A policy was established allowing for admission to the hospital of any and all patients suspected of having sustained abuse or neglect, regardless of the "medical necessity" criterion used in routine admission procedures.

The project changes have remained intact, further controlling factors that might obscure a true and actual portrait of the magnitude of our at-risk population.

Summary

Since 1977, there has been a consistent rise in the frequency of reports of child abuse and neglect generated from Mount Sinai Hospital Medical Center, Chicago. This rise is only in part due to the education of persons in control of reporting. Our study demonstrates an apparent need for the ongoing education of medical and support staff in the identification of, intervention in, and disposition of cases of child abuse and neglect. Moreover, our project illustrates the concept that any educational modality requires ongoing reinforcement and supervision. Although we were able to separate, to a large degree, factitious reporting arising from the recognition of previously unrecognized and unreported cases from the ever-increasing volume of child abuse and neglect cases, we were affected by an unexpected change in and socioeconomic condition of the country. During the course of our study, a sharp downturn of the economy and rise in the unemployment rate imposed severe social strains on a large group of already borderline and dysfunctional people. It appears that this factor had a significant effect on the incidence of abuse and neglect in our study. Continued tracking of our community has been and continues to be essential because of the demonstrated trends in child abuse and neglect. Further assessment of risk factors and the institution of preventive measures to alter the incidence of childhood maltreatment in these communities is presently underway.

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Effect of Splenectomy on the Growth of Carcinogen-Induced Experimental Bladder Cancer in Mice and Rats

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Abstract

Previous studies have shown that splenectomy has caused either retardation, no effect, or even enhancement of the growth of transplanted tumors. Since this may have significant clinical implications, we have studied the effect of prior splenectomy on carcinogen-induced primary bladder cancer in animals. This model bears a closer similarity to natural tumor growth. B6D2 F_1 mice and Fischer rats were splenectomized at 5 to 30 days and intubated at 7 to 8 weeks of age with N-butyl-N-(4-hydroxybutyl)-nitrosamine (OH-BBN). Three groups of mice of 17-22 mice each (unoperated on, splenectomized, sham-splenectomized) in which every mouse received 80 mg OH-BBN had similar incidences of tumor formation (79%–91%) and similar bladder weights and percentages of survival (12%–37%). Bladder tumors from all these groups were predominantly high-grade, extensively infiltrating squamous cell carcinomas. Three groups of rats of 14-15 rats each, in which every rat received 1800 mg OH-BBN, also had similar incidences of tumor (86%–100%), bladder weights, and survival (87%–93%). Their tumors, however, were less invasive low-grade transitional cell carcinomas. Splenectomy, thus, does not alter either the incidence or growth pattern in OH-BBN–induced bladder cancer. Because treatment with OH-BBN produces a very high incidence of primary bladder cancer in both mice and rats, we think that this is a very good model by which to study the effects of chemotherapeutic or immunotherapeutic agents on the in vivo growth of bladder cancer.

Whether the spleen is beneficial or detrimental to tumor-bearing hosts is an important clinical problem. Splenectomy has frequently been done during staging of patients with Hodgkin's disease (1) and is used therapeutically for hypersplenism or removal of disease sites. Removal of the spleen could also be useful if it were demonstrated to beneficially retard tumor growth. Splenectomy does have an effect on the incidence and degree of infection in children (2). In experimental studies on animals, investigations on the effect of splenectomy on tumor growth have yielded conflicting results. Splenectomy prior to tumor cell implantation or growth has been found to result in retardation or regression (3–11), no effect (12–15), or facilitation or enhancement of tumor growth (16, 17). The tumor inhibiting or enhancing effects of splenectomy have also been found to vary with the size of the tumor inoculum (8, 18), upon the timing of splenectomy relative to tumor cell implantation or inoculation (10), and probably with the relative immunogenicity of the tumor (6).

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Most experimental studies reporting the effects of splenectomy on tumor growth have employed tumor fragment implantation or tumor cell inoculation of the recipients as the method of choice to induce tumor growth (3–18). These secondary, transplantable tumors often grow quite rapidly on the flanks or in the ascites form, often killing their hosts within several months. We have chosen to study the effects of splenectomy on animals intubated with carcinogen because such animals develop tumors of a primary nature more slowly. The development of these carcinogen-induced primary tumors approximates more closely the development of tumors in man and may therefore be less likely to overwhelm or obscure any response to tumor growth.

In this report, we have studied the effects of prior splenectomy on N-butyl-N-(4-hydroxybutyl)-nitrosamine(OH-BBN)-induced urinary bladder cancer in mice (19) and rats (20).

Materials and Methods

Animals. Pregnant female and weanling male Fischer F344 rats were obtained from Charles River Farms, Wilmington, MA. C57BL/6 females were mated with DBA/2 males to provide B6D2 F_1 offspring. Some weanling B6D2 F_1 mice of both sexes were also purchased from Laboratory Supply, Indianapolis, Ind. Both rats and mice were housed in separate polycarbonate cages (3 rats or 5 mice/cage) and maintained at 22 ± 4°C. All animals received Formulated Chow 5008 (Ralston Purina Co., St. Louis, MO 63164) and tap water with Polyotic ad libitum.

Splenectomy. Male rats were splenectomized at 5 to 14 days of age and mice of both sexes at 28 to 30 days of age. They were first anesthetized with ether. Under aseptic conditions the spleen was exposed through a left flank incision and the organ removed. The abdominal cavity was closed with three to five wound clips. Sham-splenectomized animals of the same age underwent the same procedure except that their spleens were not removed.

Carcinogen Intubation. All animals receiving OH-BBN were first intubated at 7 to 8 weeks of age. Rats received a total dose of 1800 mg OH-BBN by gastric intubation, with 150 mg being received twice a week for 6 weeks. Mice received a total dose of 80 mg OH-BBN, also by gastric intubation, with 5 mg being received once a week for 16 weeks. All surviving animals were killed 12 months after the initial intubation with OH-BBN. All deaths occurring prior to killing were noted.

Experimental Design. All of the rats and mice were each divided into two basic groups: those intubated with OH-BBN, and those control animals that were not given OH-BBN. Each of these basic groups were further subdivided into three separate groups: not surgically treated, sham-splenectomized, and actually splenectomized. Each of the six groups of rats and of mice included from 6 to 22 animals each. Every animal from each of the six groups of both rats and mice was evaluated for the presence of tumor.

Autopsy. Immediately after death or sacrifice a laparotomy was performed on all rats and mice. Bladders were exposed and ligated in situ at the bladder neck. The ligated bladders were examined under a magnifying lens for external evidence of tumor and then excised just beneath the ligature. The excised ligated bladders were weighed immediately, distended with 10% buffered formalin, and then placed in 10% buffered formalin. Kidneys, liver, lungs, and spleen were also promptly removed, examined for tumor and placed in 10% buffered formalin. After at least 24 to 48 hours in buffered formalin, the bladders were serially sectioned and examined grossly for mucosal tumors. Sections 2mm thick of the organs were processed in the autotechnicon, embedded in paraffin, sectioned at five microns, and routinely stained with hematoxylin and eosin. Occasional sections of various tumors were stained with Alcian Blue and mucicarmine for acid mucopolysaccharides and neutral mucins, or with keratin stains to confirm the presence of keratinization.

Histopathology. Sections of all five organs were microscopically examined for the presence of tumor. Tumors from all of these organs were identified by their histological type. In addition bladder tumors were evaluated by microscopic examination for the extent of their depth of penetration of the bladder wall and for the degree of differentiation of their cells. Briefly, bladder tumors were scored as follows for their depth of penetration of the bladder: 1 noninvasive (tumor confined to mucosa); 2 superficially infiltrating (tumor extended into submucosa); 3 extensively infiltrating (tumor extended beyond submucosa into muscle); and 4 metastatic (tumor extended beyond muscle coat and invaded regional lymph nodes or formed distant metastases). The degree of cellular differentiation for each bladder tumor was also determined by microscopic examination and their cells were graded initially as follows: I for well-differentiated tumor cells; II for moderately well-differentiated cells; III for moderately undifferentiated cells; and IV for undifferentiated cells. Grades I and II were classed together as low-grade tumors, and grades III and IV were lumped together as high-grade tumors for the purposes of this study.

Statistical Analyses. All parameters, including the incidence and type of tumor, the grade and stage of tumor growth, and survival, with the single exception of bladder weights, were evaluated for significant differences between test and control groups by chi-square analysis with 2 × k contingency tables. Bladder weights were evaluated for significant differences between test and control groups by one-way analysis of variance. Any significant differences detected by the analysis of variance were further defined by the Studentized range test.

Results

Incidence and Type of Tumor. Eighty-eight neonatal mice of both sexes and seventy-three neonatal male rats were entered into the study. The incidence and types of urinary-bladder tumors formed were noted from sections made after death of the animals or at sacrifice at the end of the year-long course. Among the mice treated with OH-BBN, the incidence of bladder tumor was essentially similar for all three groups of mice—surgically naive, sham-operated, and splenectomized (Table 1). The percentage of tumor incidence for these three groups was 88%, 79%, and 91%, respectively ($p > 0.10$). Likewise, the same three groups of OH-BBN-treated rats also had similar incidences of bladder tumor formation ($p > 0.10$). These incidences were 86%, 100%, and 100% respectively. Mice and rats in the groups untreated with OH-BBN did not form bladder tumors, with a single exception. Comparison of all of the OH-BBN-treated animals with all of the untreated ones revealed that the incidence of bladder-tumor formation was significantly greater in mice and rats treated with OH-BBN ($p < 0.005$).

The types of bladder tumor formed were studied next. Forty-two of 58 OH-BBN-treated mice developed a squamous cell carcinoma of the bladder as shown by two different splenectomized mice in Figs. 1 and 2. These bladder tumors were often accompanied by keratinization and areas of focal glandular differentiation. There were no significant differences in the type of tumor ($p > 0.10$) or apparent differences in the frequency of occurrence of focal glandular differentiation in any of the three groups treated with OH-BBN. Only 8 of these 58 mice developed other kinds of neoplastic urinary bladder lesions. In contrast, carcinogen-treated rats developed exclusively transitional cell carcinomas of the bladder. This is clearly illustrated in the sections of the bladder of an OH-BBN-treated splenectomized rat (Figs. 3 and 4). No other kind of bladder tumor was detected in these rats. These transitional cell carcinomas of the bladder were often observed to be accompanied by focal areas of squamous metaplasia. No significant differences in tumor type

TABLE 1

Incidence and Type of Neoplastic Urinary Bladder Lesions Induced in Mice and Rats

	Intubated with OH-BBN*	No. of Animals	All Bladder Tumors No. (%)	Squamous Cell Ca No.	Transitional Cell Ca No.	Adeno-carcinoma No.	Other Bladder Tumors
Mice							
(B6D2 F_1)							
Surgically naive	–	13	1 (8)	1	0	0	0
Sham-splenectomized	–	6	0 (0)	0	0	0	0
Splenectomized	–	11	0 (0)	0	0	0	0
Surgically naive	+	17	15 (88)	13	0	2	0
Sham-splenectomized	+	19	15 (79)	11	2	1	1
Splenectomized	+	22	20 (91)	18	0	0	2
Rats							
(Male Fischer F344)							
Surgically naive	–	8	0 (0)	0	0	0	0
Sham-splenectomized	–	9	0 (0)	0	0	0	0
Splenectomized	–	9	0 (0)	0	0	0	0
Surgically naive	+	14	12 (86)	0	12	0	0
Sham-splenectomized	+	15	15 (100)	0	15	0	0
Splenectomized	+	15	15 (100)	0	15	0	0

* – animals did not receive OH-BBN; + animals intubated with OH-BBN.

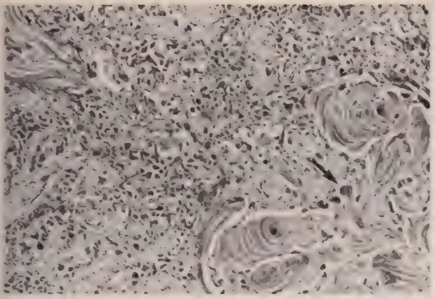

FIG. 1. Sheets of pleomorphic malignant squamous cells infiltrate between two clusters of keratinous debris containing squamous pearl. Arrow indicates largest mass of keratinous debris (H & E × 215).

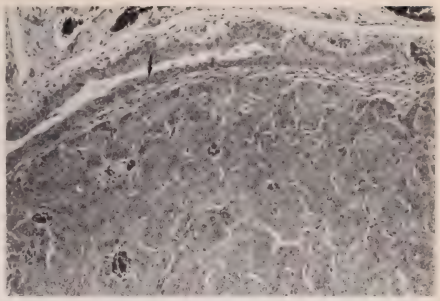

FIG. 2. Medium-power photomicrograph shows mass of moderately differentiated malignant squamous cells extensively infiltrating submucosa of bladder. Arrow indicates intact normal mucosa. Opposite wall of bladder shows normal mucosa and dilated blood vessels in submucosa (H & E × 215).

($p > 0.10$) or apparent differences in the frequency of squamous metaplasia were noted among the three groups of rats intubated with OH-BBN.

Among all of the animals subjected to treatment with OH-BBN, only five mice and no rats developed multiple malignancies. Four of these mice had renal cell carcinomas and one had a lymphoma, all of which occurred concomitantly with bladder tumors. Among the OH-BBN-untreated control mice, only one mouse from each of the three control groups developed other kinds of neoplasms. They were found to be a low-grade hepatoma, a low-grade pulmonary carcinoma, and a lymphoma. Among the untreated control rats only one developed a low-grade hepatoma.

Grade and Stage. Surgically naive, sham-splenectomized, and splenectomized animals given OH-BBN next were compared for their grade and stage of tumor growth. Splenectomized mice that developed urinary bladder tumors formed predominantly high-grade squamous cell carcinomas (Table 2). Surgically untreated and sham-operated mice also formed similar high-grade tumors, and the tumors did not differ significantly in grade with those of the splenectomized mice ($p > 0.10$). In contrast, all three groups of OH-BBN-intubated rats formed predominantly low-grade transitional cell carcinomas. The grades of the tumors from these three groups did not differ significantly ($p > 0.10$).

When the stage of tumor growth was compared among the three groups of OH-BBN-treated mice, no significant differences were found ($p > 0.10$). Most of these mice formed invasive urinary bladder tumors which infiltrated extensively through the submucosa into the muscle coat (Table 2). A few in each group formed either superficially invasive tumors of the submucosa or metastases. All of the mice formed tumors that

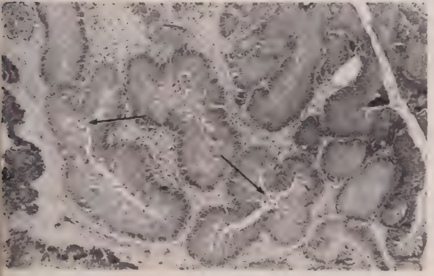

FIG. 3. Infiltrating, moderately differentiated transitional cell carcinoma displays irregular prolongations of malignant epithelium into submucosa as well as many isolated nests of tumor cells with central stellate necrosis (arrows) within submucosa (H & E × 90).

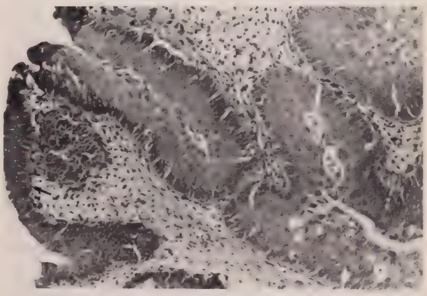

FIG. 4. Higher power magnification of Fig. 3 reveals moderately uniform transitional cells composing the tumor as well as a small segment of the normal bladder mucosa (arrow) (H & E × 215).

TABLE 2

Cellular Differentiation of Neoplastic Urinary Bladder Lesions and Bladder Tumor Growth Induced in Mice and Rats

	Number of Animals							
	Degree of Cellular Differentiation				Degree of Extension of Tumor Growth			
	Low Grade		High Grade					
	Transitional Cell Carcinoma	Squamous Cell Carcinoma	Transitional Cell Carcinoma	Squamous Cell Carcinoma	No Submucosal Invasion	Superficial Submucosal Invasion	Extensive Muscle Invasion	Metastases
Mice (B6D2 F_1)								
Surgically naive	0	1	0	11	0	1	13	1
Sham-splenectomized	2	5	0	8	0	3	7	3
Splenectomized	0	5	0	13	0	3	13	2
Rats (Male Fischer F344)								
Surgically naive	12	0	0	0	8	3	0	0
Sham-splenectomized	14	0	1	0	8	5	0	0
Splenectomized	15	0	0	0	11	3	0	0

were found to be invasive. On the other hand, all three groups of OH-BBN-treated rats formed primarily non-invasive local tumors (Table 2). A few rats in each of the three groups formed superficially infiltrating tumors of the submucosa, but no significant differences were noted in the stages of their tumor growth ($p > 0.10$). Only one rat had considerable submucosal invasion of the bladder by its tumor.

Bladder Weights. All groups of rats and mice in the study next were compared for differences in their mean bladder weights. At autopsy after death or sacrifice, bladders were removed and weighed and the mean bladder weights were recorded (Table 3). When bladder weights of the three groups of OH-BBN-treated mice or rats were compared with the three groups that did not receive OH-BBN, carcinogen treatment was found to cause a significant increase in mean bladder weight ($p < 0.001$ for either species). When just the three groups of carcinogen-treated mice were compared, it was found that the bladder weights of the splenectomized mice did not differ significantly from those of the surgically naive and sham-splenectomized mice ($p > 0.05$). Similarly, bladder weights from splenectomized rats treated with OH-BBN did not differ significantly from those of sham-operated and surgically untreated rats also intubated with OH-BBN ($p > 0.05$). Also, no significant differences in bladder weights were noted among the three groups of control mice which were not treated with OH-BBN ($p > 0.05$). Among the control rats not exposed to OH-BBN, only the sham-splenectomized animals were found to have significantly heavier bladders than either the surgically naive or splenectomized animals ($p < 0.05$). Bladder weights did not differ significantly between the surgically naive and the splenectomized control rats ($p > 0.05$).

TABLE 3

Increases in Bladder Weight in Mice and Rats Induced with OH-BBN

	Intubated with OH-BBN*	No. of Animals	Bladder Weight (gm) Mean ± SE
Mice (B6D2 F_1)			
Surgically naive	–	13	0.10 ± 0.01
Sham-splenectomized	–	6	0.08 ± 0.02
Splenectomized	–	9	0.07 ± 0.01
Surgically naive	+	13	0.54 ± 0.14
Sham-splenectomized	+	11	0.47 ± 0.11
Splenectomized	+	15	0.74 ± 0.21
Rats (Male Fischer F344)			
Surgically naive	–	10	0.15 ± 0.01
Sham-splenectomized	–	9	0.20 ± 0.04
Splenectomized	–	9	0.14 ± 0.01
Surgically naive	+	15	0.83 ± 0.21
Sham-splenectomized	+	15	0.63 ± 0.18
Splenectomized	+	15	0.42 ± 0.10

* – animals did not receive OH-BBN; + animals were intubated.

Survival. At twelve months after the onset of intubation with OH-BBN, all groups of mice and rats in the study were evaluated for their percentage of survival (Table 4). All control mice and rats that were not intubated with OH-BBN survived this period. Also, no significant differences in survival were noted among the three groups of rats treated with OH-BBN ($p > 0.10$). Only one

TABLE 4
Survival of Rats and Mice Untreated or Induced with OH-BBN

Treatment Group	Intubated with OH-BBN*	Survivors No. (%)
Mice		
Surgically naive	−	13/13 (100)
Sham-splenectomized	−	6/6 (100)
Splenectomized	−	11/11 (100)
Surgically naive	+	2/17 (12)
Sham-splenectomized	+	7/19 (37)
Splenectomized	+	5/22 (23)
Rats		
Surgically naive	−	10/10 (100)
Sham-splenectomized	−	9/9 (100)
Splenectomized	−	9/9 (100)
Surgically naive	+	13/15 (87)
Sham-splenectomized	+	14/15 (93)
Splenectomized	+	14/15 (93)

* − indicates animals did not receive OH-BBN; + indicates they were intubated.

rat each died among the sham-splenectomized and splenectomized rats, and just two of the surgically naive rats died. In contrast, many of the mice from the OH-BBN-treated groups died (Table 4), but their percentages of survival were not significantly different ($p > 0.10$). Percentages of survival among the surgically naive, sham-operated, and splenectomized mice treated with OH-BBN were 12%, 37%, and 23%, respectively.

Discussion

The spleen has many functions. Among these is the ability to kill or destroy foreign substances, such as bacteria. This organ's functions thus can be clinically significant. Removal of the organ by splenectomy often allows overwhelming sepsis and death by encapsulated bacteria, such as pneumococci (2, 21, 22). On the basis of these clinical observations, one might infer that an increased prevalence of cancer might occur in individuals who have lost splenic function.

On the other hand, several papers have suggested that the absence of a spleen is vital to the expression of anti-tumor immunity. They attribute the lack of an immune response to implanted tumor cells and subsequent tumor growth to the presence of T suppressor cells in the spleen (10, 18, 23) or to the production of enhancing antibodies (4, 6, 8). Thus, removal of the spleen would prevent the immunosuppressive effects of T splenic suppressor cells or the production of enhancing antibodies. Under these circumstances, one might expect the removal of the spleen to diminish the occurrence of cancer in individuals.

A number of studies have shown that splenectomy retards or regresses tumor growth (3–11). Other studies have shown that splenectomy has no effect or even enhances tumor growth (12–17). The conclusions that can be drawn from these studies thus remain controversial.

In the present study, we have observed that the spleen unequivocally has no effect on tumor growth in our carcinogen-treated animals. We observed no significant differences in the incidence, type of tumor, or stage and grade of tumor growth between surgically untreated, sham-splenectomized, or splenectomized mice or rats intubated with OH-BBN. Similarly, we could find no significant differences in long-term survival between these groups of carcinogen-treated animals. Also, no significant differences in bladder weights were noted among these groups of mice or rats. Among animals that were not treated with OH-BBN, no significant differences were found among any of the parameters studied, except that sham-splenectomized rats were found to have significantly heavier bladders than either surgically untreated or splenectomized rats. This result may be an artifact or it may reflect the enhancing effects of edema or other disturbances in the spleen resulting from the surgical procedure. Thus, we can clearly say within the context of the present study that splenectomy does not affect carcinogen-induced bladder cancer growth in mice or rats.

Our present study is significant and different from previous studies. In contrast to prior studies which employed transplantable tumor cell inoculation or tumor fragment implants for inducing tumor growth (3–17), we have studied the development of primary tumors in carcinogen-treated animals. The potential effects of splenectomy can probably be best observed when prior splenectomy is performed on animals which will have slowly developing primary tumors rather than rapidly proliferating secondary tumors. Carcinogen feeding or intubation can achieve this result by causing the formation of slower-growing, primary tumors. Also carcinogen induction more closely mimics the temporal relationships of primary tumor development found in man. Thus, we have used a model system which we feel reflects more accurately the natural development of tumors in man. Secondly, the results achieved in this study have been similar for both mice and rats, and thus demonstrates its applicability to more than one species. Also, the results achieved have been unequivocal in demonstrating that neither the presence nor the absence of the spleen has had a significant effect on primary bladder tumor development and growth. Finally, this study bears clinical relevance particularly to those hematologic diseases in which the spleen is removed for being a focus of neoplastic growth, or for staging, as in Hodgkin's disease (1, 2, 22), or possibly for patients who have had splenectomy for other reasons or for diseases in which the spleen may become non-functional as in sickle-cell disease (2, 21). There are no clear data at present on the development of new and different malignant tumors in patients with Hodgkin's disease after splenectomy, in patients after splenectomy for other reasons, or in patients with functional asplenia. The outcome of the present study would suggest that there may be no additional risk in splenectomized patients for the development of new malignant tumors following removal of the spleen.

The model systems we have employed in this study appear to be very useful for further studies. Treatment with OH-BBN produces a very high incidence of primary bladder cancer in both mice (19) and rats (20), as evidenced during the course of this study. The chemopreventive activity of synthetic retinoids of relatively low toxicity have been studied in OH-BBN-induced urinary bladder cancer in rats and mice (24–27). It is apparent that this model would also be very suitable for assessing the efficacy of new chemotherapeutic drugs as well as for new chemo-immunotherapeutic agents, such as tumor-specific monoclonal antibodies conjugated with toxic agents, such as ricinA (28). The highly invasive nature of the carcinomas induced by the quantitative administration of OH-BBN in B6D2 F_1 mice also provides a very useful animal model of the highly invasive variant of the human urinary bladder cancer in which to study tumor inhibition by various chemical drugs and compounds. In the present study we found that dosing with OH-BBN caused less invasive transitional cell carcinomas in rats and very highly invasive and predominantly squamous cell carcinomas in mice.

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Effects of Cryopreservation on Lymphocytes of Homosexual Men with Generalized Lymphadenopathy

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Abstract

Although both B and T lymphocytes have been shown to retain their original viability and functional activity even after several months of cryopreservation and storage, we have observed that these functions may be affected by cryopreservation. To evaluate this, we examined the proliferative and plaque-forming cell responses of lymphocytes from homosexual men with generalized lymphadenopathy (GL), and healthy controls. When the cells were cultured soon after thawing, more than 95% of the cryopreserved lymphocytes of GL patients were viable and responsed in varying degrees to in vitro stimulation with pokeweed mitogen and phytohemagglutinin. But when cultures of the thawed cells of these GL patients were delayed for six hours or more for experimental purposes—to eliminate OKT-8 positive suppressor T lymphocytes—we noticed a significant loss of viable cells and a decline in the previously observed responses to mitogenic stimulation. Similar treatment of control cells resulted in a slight decrease in the proliferative response to pokeweed mitogen. Surprisingly, the phytohemagglutinin responses of these control subjects' cells either remained the same or were slightly enhanced. The plaque-forming cell responses were not significantly altered. Treatment of fresh, unfrozen cells of GL patients and healthy controls did not result in any such loss. Thus, our studies show that cryopreserved cells, especially from patients with known immunological abnormalities, may not be suitable for certain assays and may also indicate yet another defect in the lymphocytes of homosexual men with generalized lymphadenopathy.

Cryopreservation is used extensively to store lymphocytes from normal controls and from patients, for later use in sequential studies (1–7). Both B and T lymphocytes have been shown to retain their original viability and functional activity even after several months of freezing and storage (8, 9). But in these studies, the lymphocytes were used for assays soon after thawing, without any prolonged delay between the thawing and culture procedures. During our studies of homosexual men with generalized lymphadenopathy and of asymptomatic homosexuals, we noticed that the viability and functions of cryopreserved lymphocytes were comparable to that of fresh unfrozen lymphocytes, as long as such cells were cultured within a short period after thawing. However, when we extended the time between the thawing of frozen cells and their culture, for experimental purposes, we noticed that a significant loss of viable cells occurred. By contrast, frozen lymphocytes of normal controls generally retained most of their viability and functional activity even though the time between thawing and culture was extended. Also, treatment of fresh, unfrozen cells from both the homosexual group and the normal control group did

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not result in any such loss of viability and functional activity.

Materials and Methods

Isolation of Mononuclear Cells. Venous blood from 5 homosexual men with generalized lymphadenopathy (GL), 3 healthy homosexual men, and 6 healthy heterosexual men, the control group, was anticoagulated with preservative-free heparin (heparin-sodium 10 IU/ml, from Gibco Laboratories [GIBCO], Grand Island, NY). The blood was mixed with an equal volume of saline solution, and the mononuclear cells (MNC) were isolated by the Ficoll-Hypaque (Pharmacia Fine Chemicals, Piscataway, NJ) density-gradient centrifugation method of Boyum (10). The cells were washed three times with RPMI 1640 (GIBCO) containing 5% heat inactivated fetal calf serum (GIBCO).

Freezing and Storage of MNC. Freezing and storage of MNC was done as described by S. A. Birkeland (11), with slight modifications. In brief, washed MNC were diluted in the cold freezing medium in an ice bath to give a final concentration of 5 × 10^6 cells/ml. The freezing medium consisted of 10% heat inactivated fetal calf serum (FCS), 10% dimethyl sulfoxide (DMSO), and 80% RPMI 1640. In preliminary experiments, we found that this medium gave excellent results in preserving cell viability, proliferation, and differentiation. The cells were distributed in aliquots of 1 ml in precooled plastic vials. The freezer vials were capped tightly, placed in a Cryo-Med liquid nitrogen programmable freezer (Cryo-Med, Mt. Clemens, Mich), and frozen at a rate of 1°C/min to −30°C, and then by 5°C/min to −70°C. The frozen samples were then stored in the vapor phase over liquid nitrogen (−170°C).

Thawing Procedures. The frozen samples were thawed by transferring the vials to a 37°C water bath followed by gentle continued agitation; they were removed from the bath just before the last crystal of ice in the tube melted. These thawed samples were immediately placed in an ice bath and the contents of each vial transferred to an individual 15 ml plastic centrifuge tube. The cells were diluted with cold RPMI 1640 with 5% FCS. The first 5 ml of the medium was added dropwise and the remaining tube was filled with the medium and centrifuged at 350g for 7 minutes at 4°C. The cells were washed twice, counted, and resuspended in RPMI 1640 to the desired concentration. Vital staining with 0.3% trypan blue at this time showed more than 95% viable cells. The cell suspensions were then ready for subsequent procedures.

In Vitro Treatment with OKT-8 Monoclonal Antibody and Complement. The MNC were treated either with culture medium or with complement or with OKT-8 antibody and complement as described in previous studies (12, 13). In brief, to 3 × 10^6 MNC in 0.2 ml of RPMI 1640 with 5% FCS was added 0.2 ml of OKT-8 antibody (a gift from the Ortho Diagnostic System, Raritan, NJ) at a dilution of 1:200. This solution was incubated for 45 minutes at room temperature. After incubation, fresh rabbit complement (Pel-Freez Biological, Rogers, Ark) was added to a final dilution of 1:10 and further incubated for one hour at 37°C in a humidified atmosphere. The entire procedure was repeated once more to eliminate thoroughly the OKT-8 positive subset. Altogether, this treatment took a minimum of six hours, thus delaying the culture of cells for more than six hours from the time of thawing.

Culture Conditions for Proliferation and Differentiation of MNC. The cells were cultured in RPMI 1640 with 25 mM Hepes buffer and 2 mM glutamine supplemented with 50 μg/ml gentamicin (Schering Corp., Kenilworth, NJ) as described previously (13). For the cell-proliferation assay, 10^5 cells in 0.2 ml were cultured in flat-bottom Linbro microtiter plates and the medium was supplemented with 10% heat inactivated, pooled human AB serum previously absorbed with SRBC. For B cell differentiation study, 5 × 10^5 cells in 1 ml were cultured in 12 × 75 mm Falcon tubes with 10% heat inactivated FCS. The cultures were stimulated either with pokeweed mitogen, PWM (GIBCO) or purified phytohemagglutinin, PHA (Burroughs Wellcome, Research Triangle Park, NC) at a final concentration of 1:100 and 5 μg/ml, respectively. Control cultures contained medium alone. Cell proliferation was quantified by measuring the incorporation of ^{3}H thymidine (14). The number of immunoglobulin-producing cells was determined by a modification of the Jerne hemolytic plaque assay (15, 16) using protein A coated SRBC, as described by Gronowicz et al (17).

Results

Responses of Mononuclear Cells Cultured within an Hour of Thawing. As shown in Table 1, the MNC of the patients with GL showed a reduced proliferative response to both PWM (14,475 ± 2,245 CPM/10^5 cells; mean ± SEM) and to PHA (132,385 ± 27,117 CPM) compared to the responses shown by the MNC of normal controls (PWM: 79,674 ± 14,259 CPM; PHA: 221,386 ± 15,749 CPM). The plaque-forming cell responses of these GL patients to PWM were also

TABLE 1

Responses of Frozen and Stored MNC of Homosexual Men and Normal Controls Cultured within an Hour of Thawing

Pt No.	Homosexual men with GL			Asymptomatic homosexual men		
	CPM/10^5 cells		PFC/10^6 cells	CPM/10^5 cells		PFC/10^6 cells
	PWM	PHA	PWM	PWM	PHA	PWM
1	15,750	66,873	16,200	58,441	157,116	73,840
2	7,539	88,238	0	51,840	171,398	74,080
3	21,027	218,371	14,360	99,109	165,003	79,040
4	12,266	124,320	2,320			
5	16,293	164,127	0			
Mean	14,475	132,385	6,576	69,797	164,506	75,653
± SEM	2,245	27,117	3,590	14,780	4,130	1,695
Controls (6 subjects)						
Mean	79,674	221,386	57,870	79,674	221,386	57,870
± SEM	14,259	15,749	8,296	14,259	15,749	8,296

low ($6{,}576 \pm 3{,}590/10^6$ cells) compared to the control response (57,870 ± 8,296 PFCs). The MNC of asymptomatic homosexuals showed a fairly good proliferative response (PWM: 69,797 ± 14,780 CPM; PHA: 164,506 ± 4,130 CPM) and plaque-forming cell response (75,653 ± 1,695).

Effect of Prolonged Delay between Thawing and Culture. Since the MNC of patients with GL showed a reduced proliferative and plaque-forming cell response compared to both asymptomatic homosexuals and normal controls, we thought that the reduced response could be due to the suppression of the B cell response by OKT-8 positive T suppressor cells. To investigate this possibility, the thawed and washed MNC were treated either with culture medium or with OKT-8 monoclonal antibody and complement, as described under Methods. During the treatment period, the MNC of all the patients with GL and some of the asymptomatic homosexuals—whether treated with medium or with OKT-8 antibody and complement—clumped, which resulted in a significant loss of viable cells as confirmed by trypan blue staining. The remaining viable cells were utilized for the cultures. Slight clumping was noticed in the MNCs of two of the six normal controls when their frozen cells were similarly treated.

The responses shown by the in vitro treated cells of patients with GL and asymptomatic homosexuals are shown in Tables 2 and 3. There was a significant reduction in the proliferative responses of MNC of patients with GL after treatment with either medium (PWM: 4,541 ± 1,869; PHA: 37,338 ± 12,325 CPM) or with OKT-8 antibody and complement (PWM: 1,842 ± 1,268; PHA: 11,170 ± 3,193 CPM) compared to responses shown by the untreated cells of the same subjects cultured within an hour of thawing (PWM: 14,475 ± 2,245; PHA: 132,385 ± 27,117 CPM, Table 1). In all three groups of individuals, complement-treated MNC responses were similar to those of medium-treated cells and therefore separate data for this control is not shown. Treatment of MNC of normal controls with OKT-8 plus complement resulted in a slight decrease in their proliferative response to pokeweed mitogen (47,875 ± 10,452 CPM) compared to the response of their untreated cells (79,674 ± 14,259 CPM). The response of the MNC of these individuals to phytohemagglutinin was slightly enhanced after this treatment (270,383 ± 24,941 CPM; untreated cell response: 221,386 ± 15,749 CPM). Similarly, the plaque-forming cell responses of patients with GL were also low after in vitro treatment (2,304 ± 1,259) in comparison to responses shown by their untreated cells (6,576 ± 3,590). For normal controls, there was no significant difference between the plaque-forming cell responses shown by their in vitro treated MNC (63,997 ± 13,148) and their untreated MNC (57,870 ± 8,296).

The MNC of two of the three asymptomatic homosexuals also showed a significant reduction in their proliferative responses after in vitro treatment with either medium or with OKT-8 antibody and complement compared to responses shown by untreated cells cultured within an hour of thawing. The PFC responses of the MNC of these asymptomatic persons were also reduced when they were treated either with medium (12,347 ± 11,634 PFC) or with OKT-8 antibody and complement (15,973 ± 9,258 PFC) compared to the PFC responses shown by the untreated MNC (75,653 ± 1,695).

In vitro treatment of fresh, unfrozen MNC from

TABLE 2

Responses of Frozen and Stored MNC of Homosexual Men with GL after Six-Hour Treatment

Pt. No.	With medium CPM/10^5 cells PWM	With medium CPM/10^5 cells PHA	With medium PFC/10^6 cells PWM	With OKT-8 + complement CPM/10^5 cells PWM	With OKT-8 + complement CPM/10^5 cells PHA	With OKT-8 + complement PFC/10^6 cells PWM
1	490	9,358	640	399	9,902	7,120
2	773	13,077	640	0	3,051	320
3	3,787	45,061	1,680	1,136	13,540	1,360
4	7,848	42,048	1,600	821	18,186	400
5	9,808	77,148	400	6,856	not done	2,320
Mean	4,541	37,338	992	1,842	11,170	2,304
± SEM	1,869	12,325	268	1,268	3,193	1,258
p*	<0.01	<0.05	>0.05	<0.01	<0.01	>0.05
Controls (6 subjects)						
Mean	36,150	262,848	29,315	47,875	270,383	63,997
± SEM	12,490	23,522	9,141	10,452	24,941	13,148

* In comparison to mean responses shown by untreated MNC of homosexual men with GL, presented in Table 1.

two homosexual men with GL, either with medium or with OKT-8 antibody and complement, did not result in any clumping and loss of viable cells. However, significant clumping and loss of viability were noticed when MNC that had been frozen and stored overnight were similarly treated (data not shown), as observed with frozen MNC of other GL patients.

Discussion

Cryopreservation of lymphocytes from normal healthy persons and from patients with various diseases has been successfully used for assays of immunological functions without any appreciable loss of cell viability and functional activity. This was achieved mainly because frozen cells were cultured within a short time after thawing. The present study shows, however, that cryopreservation can harm lymphocytes under certain circumstances. The frozen and stored MNC of homosexual men with generalized lymphadenopathy and of some asymptomatic homosexual men consistently showed excessive clumping and loss of viability when culturing of the cells was delayed for more than an hour after thawing. Minute clumps were noticed even in some of the normal heterosexual control MNC. Similarly, reduced proliferative and plaque-forming cell responses were seen in the patients with GL and asymptomatic homosexuals. This occurred during in vitro treatment of the frozen cells with OKT-8 antibody plus complement, with complement, or even with culture medium, and was not observed with unfrozen cells from either patients with GL, homosexual controls, or normal heterosexual persons.

Loss of viable cells during in vitro treatment,

TABLE 3

Responses of Frozen and Stored MNC of Asymptomatic Homosexual Men after Six-Hour Treatment

Pt. No.	With medium CPM/10^5 cells PWM	With medium CPM/10^5 cells PHA	With medium PFC/10^6 cells PWM	With OKT-8 + complement CPM/10^5 cells PWM	With OKT-8 + complement CPM/10^5 cells PHA	With OKT-8 + complement PFC/10^6 cells PWM
1	1,312	5,619	0	2,315	5,812	8,960
2	29,005	128,445	35,600	32,742	137,926	34,320
3	8,134	30,881	1,440	1,909	56,392	4,640
Mean	12,817	54,982	12,347	12,322	66,710	15,973
± SEM	8,330	37,449	11,634	10,211	38,485	9,258
p*	<0.05	<0.05	<0.01	<0.05	>0.05	<0.01
Controls (6 subjects)						
Mean	36,150	262,848	29,315	47,875	270,383	63,997
± SEM	12,490	23,522	9,141	10,452	24,941	13,148

* In comparison to mean responses shown by untreated MNC of asymptomatic men, presented in Table 1.

with a resultant decrease in the number of viable cells in the final cultures, could explain the reduced proliferative and plaque-forming responses noticed in the MNC of patients with GL and asymptomatic homosexuals. It is interesting to note, however, that the proliferative responses of frozen MNC of normal heterosexual controls to pokeweed mitogen were considerably reduced after in vitro treatment, as against their normal or even enhanced responses to phytohemagglutinin. If the reason for the observed reduction in the response to pokeweed mitogen was cell death which occurred during in vitro treatment, then one might also expect a reduced response to phytohemagglutinin. But this did not occur. Moreover, among these controls the plaque-forming cell response to pokeweed mitogen was also not significantly altered after treatment with OKT-8 antibody and complement, although it was considerably reduced in the cells treated with medium. The reason for these findings is not clear but suggests that a phytohemagglutinin-responding subset of T cells may be more resistant to damage during in vitro treatment of frozen cells.

To what extent an intrinsic cellular abnormality, an acquired defect in the cell, or a combination of both produced the clumping and loss of viable cells is not known. Since clumping and loss of viable cells were observed only when frozen cells were used, not under similar conditions with fresh, unfrozen MNC, it would appear that freezing and thawing of intrinsically abnormal cells are critical factors leading to cell death. Prolonged delay in the culture of such damaged or susceptible cells could have stressed the cells sufficiently for unknown causes to produce their death.

It is also possible that the cryoprotectant dimethyl sulfoxide, which was used to prevent freezing damage to the lymphocytes, may have affected the cells. DMSO has been shown to have a toxic effect on cells in the frozen state (18). Baxter and Lathe (19) have shown that DMSO can interact with the lysine-rich control enzyme within the cell and block glycolysis even after its removal from the cell. If so, the lymphocytes of homosexuals with GL may be more sensitive to DMSO than the lymphocytes of normal controls. Further studies are needed to investigate this possibility.

However the abnormality was acquired, one should be aware of this problem before attempting to freeze and store lymphocytes from such patients for future assay of their immunological functions. The problem should also be considered in relation to patients having other known immunological disorders, since it is possible that similar, as yet undetected defects may exist in their lymphocytes.

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Iron Absorption and Utilization in Maintenance Hemodialysis Patients: Oral and Intravenous Routes

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Abstract

Nine patients (Group A) on long-term hemodialysis were studied by whole-body counting and isotope ferrokinetics to determine their absorption of oral iron and incorporation of the absorbed iron into their red blood cells. These patients as well as 5 other long-term dialysis patients (Group B) had ferrokinetic studies after administration of intravenous iron dextran. Group A patients had normal absorption of orally administered iron (13.1 ± 8.7%); however, they evidenced delay in the number of days required for maximum red cell incorporation (RCI) of iron to 33.8 ± 15 days, and maximum RCI was 65.7 ± 24.3% (normal 80%). Group B patients demonstrated normal maximal RCI (91.3 ± 12.7%) and normal number of days to reach maximal RCI (8.6 ± 3.6). Group A patients showed no improvement in hematocrit after oral iron therapy; however, both Group A and Group B patients had increases in hematocrit after parenteral iron therapy. The reason for the poorer response to oral as compared to parenteral iron therapy in these patients requires further study.

Patients with chronic renal failure develop moderate to severe anemia which is only slightly improved by maintenance dialysis. The anemia is primarily due to deficient production of erythropoieton; however, other factors contributing to the anemia include reduced red cell life span and blood loss during dialysis (1). It has been estimated that the hemodialysis procedure results in annual blood loss equivalent to 1 to 2 grams of iron (2). The normal total body iron store is 3–5 grams; thus iron deficiency may occur in patients on chronic maintenance dialysis when transfusion is avoided and iron supplements are not given. Controversy exists regarding efficacy of oral and parenteral iron therapy in improving the anemia in maintenance dialysis patients and the present study was undertaken to evaluate gastrointestinal iron absorption and the utilization of orally administered iron and to compare the red cell incorporation of oral and parenterally administered iron. We have used a whole-body counter to measure iron absorption in order to obtain the most satisfactory means of measurement (3).

Methods

Fourteen patients whom the dialysis staff believed to be good drug compliers on regular maintenance dialysis therapy for over three months were studied. All were dialyzed 5–6 hours three times a week using coil dialyzers; the coils were not reused. The patients did not receive any iron therapy or blood transfusions for at least eight weeks prior to this study. All patients were receiving a daily diet of 60 gm high biologic value protein, 2 gm Na, and 2 gm K, together with B complex with C vitamins and folic acid supplement. Aluminum hydroxide was administered to

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control hyperphosphatemia. None of the female patients were menstruating. None of the patients except one (Patient 11) had any gastrointestinal surgery, peptic ulcer disease, malabsorption, or infection. Patient 14 had partial gastrectomy for peptic ulcer. All of the patients had negative stools for occult blood and no other evidence of blood loss. All the patients had normal serum bilirubin, negative Coomb's test, normal serum haptoglobin, normal serum B_{12}, and normal RBC folate.

Patients were divided into two groups. One group (Group A) was studied while receiving oral iron therapy and the other group (Group B) was studied while receiving intravenous iron dextran therapy.

Group A patients had iron absorption determined by orally ingesting a solution composed of 10 μCi Fe^{59} in 0.1 mg ferric citrate, 10 mg ferrous sulfate and 50 mg ascorbic acid dissolved in 200 ml of distilled water after an overnight fast. The patient continued to fast for 4 hours after ingestion of this solution. At this point whole-body counting for Fe^{59} was carried out; the value obtained was considered to represent 100% of the administered dose. Background activity of each patient was measured before administration of solution. Whole-body counting was repeated 14 days later and expression of iron absorption as a percentage of the ingested dose was determined.

After the initial whole body count was made, Group A patients were begun on oral ferrous sulfate 325 mg three times a day 1 hour before meals for 3 months. At the time of the initial whole-body count, red cell mass was measured by ^{51}Cr red cell tagging. Blood specimens were obtained every 3 days for 14 days and then once weekly for an additional 8 weeks, and Fe^{59} activity of blood was determined. From the ratio of Fe^{59} activity to the red cell mass at each determination (with correction for decay) the red cell incorporation of iron (RCI), that is, the percentage of absorbed Fe^{59} present in the erythrocyte at the time of each determination, was determined. After 3 months of oral iron therapy, Group A patients were given Imferon 100 mg intravenously monthly as in Group B.

Group B patients received 100 mg of iron dextran (Imferon) once a month for 3 months by infusion into the venous blood line at the termination of a hemodialysis. At the time of the first infusion 10 μci Fe^{59} was administered intravenously. Red cell mass was determined by ^{51}Cr studies and RCI was determined in a manner similar to that described for Group A.

Hematological parameters, including complete blood count, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), hematocrit, serum iron, and iron binding capacity, were measured by automated methods monthly. Bone marrow specimens were obtained by iliac crest puncture, stained for iron with Prussian blue where presence of iron was graded in the bone marrow in the scale 0 to 4+ (0 being absent, 1+ being normal status, and 4+ being excessive iron).

Whole Body Count Method. The patients were counted in the Hines V.A. Hospital whole-body counter which is constructed of armour plate steel with inside dimensions of 7 ft × 7 ft × 10 ft. Contained in the facility is an "Argonne chair" arrangement for maintaining reproducibility of patient positions and geometry. The geometry system uses the principle of the 50-cm radius vector averaging body mass above and below this point. A 4 in × 8 in sodium iodide detector was used which was viewed by three 3-in quartz windowed photo multiplier tubes giving a total background from 10 KeV to 1 MeV of 2.85 counts/min cc of crystal. The data was collected by a Nuclear Data 2200 system with 512 Channels and a calibration of 10 KeV/channel. A window was so arranged about the 1.097 and 1.289 photopeak as to encompass energies from 600 KeV to 1400 KeV to eliminate the effects of Compton interactions.

Although each patient was used as his own standard by counting him first at the time of administration which represents the 100% absorption point, an Fe^{59} standard containing 500 Ml of deionized water in a 500 ml polyethylene bottle was placed on a stainless steel bridge across the seat of the chair. This was for the purpose of normalizing the counts due to decay from week to week and took into account small variations in instrument operation.

Results

Hematological data, % iron absorption and RCI are shown in Table 1.

Absorption of the orally administered radioactive iron in Group A patients varied from 4.36% to 30% when measured 14 days after ingestion of the tracer dose. Mean absorption was 13.1% ± 8.7%, which is within the range of normally reported absorption (5%–10%) (4). One patient was found to have 92.9% absorption.

Maximum RCI of absorbed iron in Group A patients varied from 33.7% to 100%, with a mean RCI of 65.7 ± 24.3 (normal 80%); only 3 of the 9 patients in this group had normal RCI. Normally RCI is maximum at 14 days; Group A patients demonstrated a range of 7 to 50 days to reach maximum RCI with a mean of 34 ± 15 days.

TABLE 1

Clinical and Laboratory Data on Study Population

Patient No.	Age/Sex	Diagnosis	Initial Hct.	Serum Iron	TIBC	Bone Marrow Iron	Iron Abs%	Max RCI	Days to Max RCI
Group A									
1	35/M	Obstructive uropathy	18.9	62	327	4+	4.4	91.4	7
2	48/F	Nephrosclerosis	16.0	49	269	3+	4.6	94.8	10
3	29/M	Glomerulonephritis	28.2	57	249	3+	6.1	100.0	42
4	40/F	Glomerulonephritis	17.9	40	169	4+	30.0	37.0	42
5	55/F	Interstitial nephritis	20.5	66	208	3+	19.6	57.3	36
6	65/M	Interstitial nephritis	22.5	112	337	4+	11.0	57.1	41
7	65/F	Interstitial nephritis	20.1	80	293	1+	14.2	60.6	34
8	68/F	Nephrosclerosis	16.3	64	312	2+	15.4	33.7	50
9	52/F	Chronic pyelonephritis	35.5	26	322	0+	92.9	60.1	43
Mean			21.7	61.8	276.1		13.1*	65.7	33.8
+ S.E.M.			± 2.1	± 8.2	± 19.3		± 8.7	± 24.3	± 15
Group B									
10	39/M	Diabetic nephropathy	24.0	70	143	4+		84.7	6
11	32/M	Obstructive uropathy	26.3	87	264	0+		100.0	7
12	64/M	Interstitial nephritis	20.4	64	223	2+		71.9	15
13	50/F	Nephrosclerosis	28.5	84	266	3+		100.0	7
14	46/M	Nephrosclerosis	23.9	46	476	3+		100.0	8
Mean			24.6	70.2	224			91.3	8.6
± S.E.M.			± 1.3	± 7.4	± 55			± 12.7	± 3.6

TIBC = total iron binding capacity.

Iron Abs% = % Fe^{59} retention after 14 days from orally administered dose.

Max RCI = Maximum red cell incorporation of absorbed Fe^{59}.

* excluding Pt. 11.

Thus Group A patients appeared to have adequate absorption of orally administered iron but a decreased RCI and a delay in achieving maximum RCI.

There was no correlation between total iron binding capacity, transferrin % saturation, serum iron, or hematocrit with iron absorption. There was also no correlation between bone marrow iron stores and either maximum RCI or number of days required to reach maximum RCI. However, there is a significant negative correlation between bone marrow iron status and oral iron absorption ($R = -0.67, p < .001$).

Maximum RCI in Group B (intravenous iron) varied from 71.9% to 100% (mean 91.3 ± 12.7), and maximum RCI occurred between 6 and 15 days (mean 8.6 ± 3.6). One patient with absent stainable iron in the marrow (No. 14) had prompt and full incorporation of intravenous iron. Thus Group B patients appeared to have normal amounts of iron incorporated into red cells and an accelerated time of reaching full incorporation.

There was no rise of hematocrit in Group A patients after 3 months of oral iron (Table 2). Group B patients showed a rise of hematocrit of 4.1 ± 2.3% after three months of intravenous iron dextran therapy. A subsequent three-month course of intravenous iron dextran in Group A patients following completion of oral iron therapy showed a rise in hematocrit similar to that in the Group B patients.

Discussion

Several authors have drawn attention to the development of iron deficiency as a component of the anemia of chronic renal failure in patients receiving long term hemodialysis (1, 2, 5, 6). This iron deficiency is related to the inevitable loss of small quantities of blood (approximately 20cc) that occurs with each dialysis treatment. Studies suggest most dialysis patients lose up to two grams of iron per year while on dialysis (1, 2). However, controversy exists regarding effective-

TABLE 2
Effect of Oral and Intravenous Iron Therapy on Hematocrit (HCT)

Pt. No.	Baseline HCT	HCT after Oral therapy (3 months)	HCT after IV therapy (3 months)
Group A			
1	18.9	17.5	19.2
2	16.0	17.4	21.3
3	28.2	26.7	35.6
4	17.9	16.7	22.1
5	20.5	22.4	23.4
6	22.5	20.8	26.2
7	20.1	19.7	22.3
8	16.3	15.8	19.5
9*	35.5	32.0	38.1
Group B			
10	24.0		21.1
11*	26.3		30.3
12	20.4		22.7
13	28.5		30.5
14	23.9		31.6

* Absent marrow iron at start of study.

ness of oral and parenteral iron therapy in correction of this iron deficiency. Brozovich et al have demonstrated that oral iron is absorbed in chronic renal failure but these subjects did not replenish marrow iron stores although there was some improvement in hematocrit (7). The present study using a whole-body counter demonstrates that patients on chronic hemodialysis are able to absorb iron satisfactorily. A study by Esbach et al showed that oral iron absorption as determined by serum iron and iron binding capacity is influenced by the iron balance of patients rather than the presence or absence of uremia, anemia, or the rate of erythropoiesis (8). Other studies using serum ferritin levels and marrow iron stores have confirmed these findings (9). Indeed, the one patient we had with absent iron marrow had 92% iron absorption confirming these findings. Studies by RA Carter et al suggest that parenteral iron therapy increases HCT and RBC mass and enhances iron utilization by the marrow (5). Our patients demonstrated a rise in hematocrit after intravenous iron therapy regardless of the status of the marrow iron stores at the times of initiation of parenteral iron. Others have reported findings similar to ours (10). Although there was little change in the hematocrit in the Group A patients treated with three months of oral iron therapy, when these patients were subsequently given intravenous iron, they responded with a similar increase in hematocrit.

Oral iron absorption in our patients was good (Table 1); however, there was a striking difference in utilization of the iron for oral and parenterally administered iron as measured by red cell incorporation of iron. Although 65% of absorbed oral iron was incorporated into red cells, over 90% of intravenously administered iron was incorporated. In our study we also found that iron administered orally takes much longer than parenteral iron to be maximally utilized in forming hemoglobin (34 days versus 8 days). The utilization of oral iron in our patients is similar to that previously reported (11); the reason for more rapid utilization of parenteral iron therapy requires further study.

This study suggests that parenteral iron is better utilized than oral iron in patients on maintenance hemodialysis. During the course of this study, no side effects of intravenous iron administration were noted. Further study is required to determine the ideal dose and frequency of administration of parenteral iron.

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Stereologic Analysis of Muscle Capillaries in Selective Atrophy of Type 2 Myofibers

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Abstract

To find out what happens to muscle capillaries in selective atrophy of type 2 myofibers, we used stereologic techniques to estimate muscle capillaries in muscle biopsies of 11 patients with type 2 atrophy from various causes. We compared these capillaries with others from a control group of 6 patients with suspected but unproved neuromuscular disorders. Volume, surface, length, and numerical profile densities of capillaries were higher in type 2 atrophy, but the numerical ratio of capillaries to myofibers did not differ from controls. Transverse area of a myofiber was smaller in type 2 atrophy, but the volume density of myofibers and interstitial collagen did not differ in the two groups. Our findings indicate that there is capillary hypervascularity in selective atrophy of type 2 myofibers.

Selective atrophy of type 2 fibers is a common biopsy finding, but very little is known of its capillary supply. In this study, we compared stereologic estimates of muscle capillaries of patients with type 2 atrophy with similar estimates of control patients. Our findings show that there is an increase in the capillary supply of skeletal muscle with type 2 atrophy.

Methods

Eleven men and women with selective atrophy of type 2 fibers from various causes and a control group of six men and women with suspected but unproved neuromuscular disorders constituted the subjects of the study.

Biopsy specimens were cut with a razor blade into 2 to 4 blocks and frozen in isopentane at −160°C. Next, serial or step transverse sections were cut at eight micrometers and stained with modified trichrome and myosin adenosine triphosphatase (ATPase) pH 9.4 stains (1). Diameters and the atrophy and hypertrophy factors of type 1 and type 2 myofibers were estimated on sections stained with myosin ATPase pH 9.4 with our modification (2) of Brooke and Engel's method (3).

Aside from an abnormally high atrophy factor, the biopsies of patients with type 2 atrophy showed no other abnormalities. Likewise, those in the control group showed no morphologic or enzyme histochemical abnormalities.

Subjective histologic estimates of sections stained with modified trichrome showed more myofibers and capillaries per high power field in type 2 atrophy, compared to sections from controls, and an apparent decrease in the numerical ratio of capillaries to myofibers in type 2 atrophy. We observed no difference in the size of capillaries in the two groups.

Table 1 lists the clinical and biopsy findings of both groups of patients.

Stereologic Methods. We used point and line intersection counting techniques of stereology (4) on sections stained with modified trichrome to quantitatively estimate muscle capillaries, myo-

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TABLE 1

Suspected Diagnosis and Biopsy Findings

Pt. No.	Age/ Sex	Muscle*	Type 2 Diameter (μm)	Atrophy Factor	Reason for Biopsy
ype 2 atrophy					
1	19M	VM	51.9	250	R/O polymyositis
2	20F	leg	34.7	610	R/O polymyositis
3	37F	leg	22.1	1340	R/O polymyositis
4	40M	VM	43.0	570	R/O myasthenia gravis
5	40F	VM	42.4	340	R/O polymyositis
6	43F	VM	35.9	450	Steroid myopathy
7	53M	VM	49.4	590	Steroid myopathy
8	58M	VM	50.2	570	Diabetic amyotrophy
9	60F	leg	37.7	310	R/O dystrophy
10	60M	VM	52.1	1020	R/O polymyositis
11	63M	VM	42.6	530	R/O polymyositis
ontrols					
12	21F	—	61.5	20	R/O polymyositis
13	21M	leg	58.8	50	R/O McArdle's disease
14	22F	leg	62.2	0	Leg pain
15	28F	D	41.1	20	R/O myopathy
16	35F	leg	41.7	70	Leg pain
17	36M	D	52.6	90	R/O polymyositis

* VM = vastus medialis; D = deltoid.

fibers and interstitial tissue. A test grid in the eyepiece of the microscope (see Fig.) was used to sample, with the 40× objective, at least seven fields by moving the stage of the microscope. This was done without looking at the section and the field was then checked to make sure that the same field was not counted twice. Counts were done on as many sections as possible.

The points (upper right-hand corner of squares in grid) hitting capillary lumina and their wall, myofibers, and interstitial collagen were counted in each field. Volume density V/V of capillaries, myofibers, and interstitial collagen was estimated using a derivation of Delesse's equation $V/V = P/P$, where P/P is the point fraction of the histologic component. P/P was obtained by dividing the total points hitting the histologic component by the total points hitting the reference component, which was either myofiber or muscle tissue itself.

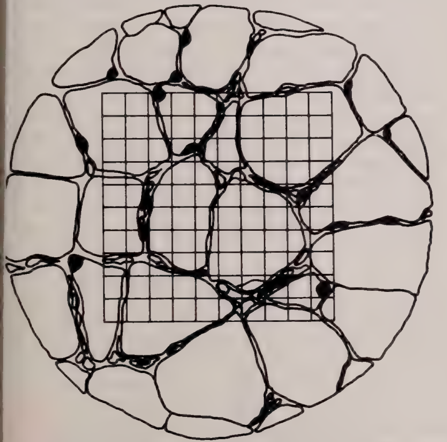

FIG. Drawing attachment tracing showing grid overlying myofibers, interstitial tissue and capillaries on modified trichrome stained section. Capillaries are the circular, oval, and twisted profiles between the muscle fibers. Side of squares of the grid is 25 micrometers in this tracing.

Next, we counted the number of intersections of the profile of the lumina of capillaries with the horizontal lines (tops of the squares) of the grid. Surface density S/V was estimated as $S/V = 2I/L$, where I is the number of intersections and L is the total line length. The total number of points hitting myofibers or muscle tissue was equal to the total line length in our grid.

The number of profiles of capillaries and of myofibers were then counted in the grid. For the myofibers, the count was divided into those hitting the sides of the frame of the grid and those completely within the grid. Length density J/V was estimated as $J/V = 2Q/A$, where Q is the number of capillaries within the grid and A is the transverse area of myofibers. The latter was equal to the number of points hitting myofibers times 625 μm^2 (square of the length of the side of the squares in the grid). Numerical profile density on area was estimated as N/A by dividing the number of capillaries, N, by the transverse area of myofibers, A. Adjusted number of myofibers was estimated using the formula for edge effect $N/A = (N^* + N/2)A$, where N^* is the number of fibers hitting the edge of the grid, N is the number of fibers within the grid, and A is the transverse area of myofibers. Numerical ratio of capillaries to myofibers was estimated using the adjusted number of myofibers in the test grid. Last, the transverse area of a myofiber was estimated by dividing the transverse area of myofibers, A, by the adjusted number of myofibers.

The standard error of the mean (SEM) of J/V, N/A, numerical ratio of capillaries to myofibers, and transverse area of a myofiber was obtained from the estimates of the fields counted, using standard statistical tests. The standard error (SE) of the volume density (V/V) was estimated as $SE = \sqrt{p \times (1 - p)/n}$ where p is the point fraction P/P and n is the total number of points. This assumes a binomial distribution for the hits on capillaries because the average diameter of capillaries was less than the side of the squares of the grid, thus assuring that each capillary was hit by a point independently. SE of $S/V = 2\sqrt{I}/L$ on the

TABLE 2

Stereologic Estimates of Type 2 Atrophy and Controls

	Type 2 Atrophy (n = 11)	Controls (n = 6)
Capillaries		
Volume density (mm^3 100 mm^3)	1.2 ± 0.2* 1.0, 0.6–2.8	0.6 ± 0.1* 0.5, 0.4–0.9
Surface density (mm^2 100 mm^3)	683 ± 98** 620, 257–1437	253 ± 52** 236, 114–432
Length density (mm 100 mm^3)	42300 ± 2100 43300, 27900–54400	34300 ± 4600 35800, 14800–43800
Numerical density (n mm^2)	212 ± 11 216, 139–272	177 ± 26 179, 73–249
Capillary myofiber Ratio (n 100)	85 ± 6 82, 60–122	89 ± 10 86, 45–112
Myofiber		
Area (μm^2)/myofiber	4171 ± 365* 4089, 2419–6333	5406 ± 443* 5303, 4016–6541
Volume density (mm^3 100 mm^3)	90.9 ± 0.8 90.6, 86.4–95.6	90.0 ± 2.0 91.3, 80.3–93.3
Perimysial collagen		
Volume density (mm^3 100 mm^3)	3.9 ± 0.8 2.9, 0.4–8.6	5.7 ± 0.2 3.7, 2.8–16.1
Endomysial collagen		
Volume density (mm^3 100 mm^3)	4.1 ± 0.3 3.8, 2.3–6.9	3.9 ± 0.3 3.6, 2.7–5.0

Estimates of capillary densities expressed per volume or area of myofibers. All other densities expressed per volume of muscle tissue. Estimates given as mean ± standard error of the mean, median, and range.

* $P < .05$, ** $P < .01$.

assumption that the distribution of I was a Poisson distribution. This assumption was also made because of the smaller size of capillaries compared to the lines of the grid.

Results were analyzed using standard statistical tests programmed on an Apple II Plus computer.

Results

We compared the mean, median, and range of stereologic estimates of capillaries, myofibers, and interstitial collagen in biopsies from patients with type 2 atrophy and from controls (Table 2). Mean volume and surface densities were significantly higher in type 2 atrophy. Mean length density and numerical profile density on area were 20% higher in type 2 atrophy, but the difference was not significant. The mean numerical ratio of capillaries to myofibers did not differ in the two groups. In contrast, the mean transverse area of a myofiber was significantly less in type 2 atrophy. Mean volume density of myofibers and interstitial collagen also did not differ in the two groups.

Discussion

Our results can be simply explained as follows: (a) because the transverse area of a myofiber was smaller in cases of type 2 atrophy, and the relative volume of myofibers and interstitial collagen did not differ in the two groups, more myofibers were included in the test grid in type 2 atrophy; (b) because the numerical ratio of capillaries to myofibers did not appear to change with the atrophy of type 2 myofibers, more capillaries were "pulled" into the grid, causing the 20% increase in the numerical profile density of capillaries in type 2 atrophy; (c) because length density is derived from numerical profile density, the length density of capillaries also increased in type 2 atrophy; and (d) with more capillaries within the test grid, the chance of the test probes, that is points and lines, hitting capillaries increased in type 2 atrophy and this resulted in the higher volume and surface densities of capillaries in type 2 atrophy. But an increase in the size of capillaries could also cause the volume and surface densities to increase. We think that this possibility is unlikely, however, because our subjective histologic estimates did not show bigger capillaries in type 2 atrophy. It appears, therefore, that the increase in the volume and surface densities of capillaries resulted from the increase in the numerical profile density of capillaries in type 2 atrophy, which in turn was the result of the atrophy of type 2 myofibers itself. It should also be pointed out that the results of our stereologic and subjective histologic estimates were similar.

Our findings, therefore, indicate that there is a capillary hypervascularity in selective atrophy of type 2 myofibers. Moreover, it appears almost certain that this capillary hypervascularity results from the atrophy of myofibers itself. It is not clear, however, how the capillary vascular bed of skeletal muscle reacts to atrophy of myofibers.

In atrophy of myofibers caused by aging, Parizkova et al (5) found that the numerical ratio of capillaries to myofibers decreased although the numerical profile density of capillaries did not change. They concluded that there was no change in the capillary supply of myofibers rendered atrophic by aging. In atrophy of skeletal muscle caused by spontaneous rupture of its tendon, Jozsa et al (6) reported a rapid decrease in the numerical ratio of capillaries to myofibers—to half within two weeks and to almost two thirds two months after the injury. In addition, the atrophic muscle showed less branching and anastomosis of its capillaries. The authors concluded that there was a decrease in the capillary supply of skeletal muscle after spontaneous rupture of its tendon. In contrast, Carpenter and Karpati (7) reported that the numerical profile density of capillaries increased in denervated muscle as the numerical ratio of capillaries to myofibers decreased because of loss of capillaries through necrosis. They suggested that denervated muscle becomes relatively overvascularized. In a previous stereologic study of plastic-embedded sections of skeletal muscle, we (8, 9) found that the numerical ratio of capillaries to myofibers, numerical profile density, surface density, and volume density of capillaries were higher in the atrophic areas of muscle biopsies of patients with inclusion-body myositis compared to random areas of the same biopsy. We concluded that the capillary hypervascularity of atrophic myofibers in that disorder resulted from the atrophy of myofibers itself.

We have no explanation why the capillary vascularity of skeletal muscle appears to differ in different types of atrophy of myofibers. Certainly, the rate and severity of the atrophy should be considered. However, the possibility of bias introduced by the techniques used, including stereology, should not be overlooked (10).

Possibility of Bias. Stereology is a statisticogeometric system that attempts to predict the three dimensions of structures in space from their sections which are in two dimensions or less. Estimates of the relative volume, surface area, length or number of histologic components in an organ can be obtained from simple counts on histologic sections. In properly designed studies, unbiased or true estimates can be obtained (4), but in clinical studies unbiased estimates are not easy to get because sampling is often less than optimal. Stereologic study of skeletal muscle is further biased by the preferential orientation of the myofibers and capillaries. In stereologic terms, skeletal muscle is an anisotropic structure, and in such structures, estimates of the length and surface density are likely to be biased unless the degree of anisotropy is considered (4, 10). To estimate the degree of anisotropy of skeletal muscle, however, is laborious and probably impractical in clinical practice (10). Thus, there are several sources of bias in stereologic study of skeletal muscle which cannot easily be corrected in clinical studies. Nonetheless, comparison of estimates even if they are biased can provide information not otherwise attainable in clinico-pathologic studies. This is particularly true if, as in this study, there is no reason to suspect that the bias will differ in the groups being compared.

We conclude, therefore, that there is a capillary hypervascularity in selective atrophy of type 2 myofibers and that the hypervascularity probably results from the atrophy of myofibers itself.

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Renal Dysplasia and Chondrodysplasia in the ch Hydrocephalic Mouse: A Cellular Model of Defective Differentiation and Organization

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Abstract

From previous quantitative analysis of the developing sternocostal cartilage in mice with the recessively inherited ch gene and hydrocephalus, we have shown that the acidic glycosaminoglycan (proteoglycan) concentration, being mainly chondroitin sulfate, is 40 ± 3% of that of the normal (control) satin mouse. From corresponding histochemical examinations in all three genotypes, decreased acridine orange fluorescence of the ch murine sternum represented fewer available extracellular polyanionic binding sites. Ultrastructurally, the peripherally located ch mesenchymal sternal cells appeared fibroblastic and never differentiated into chondrocytes. The ch intercellular matrix contained a paucity of electron-dense granules (proteoglycans) and collagen fibrils. But the extracellular collagen fibrils which were present either aggregated abnormally or formed enlarged collagen fibrils due to a deficiency of polyanionic (proteoglycan) matrix substances. We proposed that the failure of endochondral ossification is due to a principal failure of mesenchymal differentiation. Similar findings of failure of mesenchymal differentiation and of cellular disorganization were also found in the ch murine renal system. This research may help characterize the molecular locus of this multisystemic genetic defect and may aid in the understanding of the human proteoglycan disorders (mucopolysaccharidoses).

Congenital hydrocephalus is a known complication of the inherited disorders of mucopolysaccharide (proteoglycan) metabolism (1, 2). In the case of human systemic mucopolysaccharidoses, subclinical or asymptomatic hydrocephalus is frequently observed at autopsy, as well as clinical involvement of and defects in the musculoskeletal, renal, and cutaneous systems (1–4). Mice of the ch strain have a congenital, recessively inherited, lethal hydrocephalus that can be demonstrated prenatally in association with multiple developmental defects in cartilaginous or endochondral bone formation (Fig. 1), and with cutaneous and renal anomalies (1–7). These ch hydrocephalic mice are usually dead at birth, or die within a few minutes following birth, probably due to asphyxia related to defective tracheal cartilage (5–7).

Our experimental purposes were to investigate the genetic defects of the ch hydrocephalic mouse and correlate these with the multisystemic defects of the human proteoglycan (mucopolysaccharide) disorders. This present research consisted of investigation of the gross, microscopic, and ultrastructural anatomy in the developmental failure of the cartilaginous system and

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the subsequent failure of endochondral ossification of the ch mouse's sternum. In our previous work we had shown quantitatively that the developing sternocostal cartilage of the recessive ch hydrocephalic mouse has 40 ± 3% of the acidic glycosaminoglycans concentration of the normal satin control mouse (+sa/+sa) and that this condition is qualitatively associated with decreased metachromasia with alcian blue staining, diminished fluorescence with acridine orange staining, and subsequently decreased polyanionic binding in the extracellular space of the ch sternum (1). In studying other systems of the ch mouse, we noticed definitive gross and microscopic changes in the renal system, and we identified similar developmental errors in both renal and cartilaginous systems.

Materials and Methods

The mice used were from sibling matings of heterozygotes carrying the linked marker satin (sa) gene "in repulsion" (ch+/+saxch+/+sa) (7). In the ch strain, a satin marker has been introduced into chromosome 14; this satin coat marker is used to distinguish the normal nonhydrocephalic (+sa/+sa) mice from the heterozygotes or trait carriers (ch+/+sa) (7). Three types of offspring were produced: (a) homozygote recessive for the ch gene (ch+/ch+), 25%; (b) heterozygote for both the ch and sa genes (ch+/+sa), 50%; (c) homozygote for the sa gene (+sa/+sa), 25% (7, 8). The latter group of mice had abnormal hair texture, giving their coats a satinlike appearance, which made visual identification possible after their coats formed (1). Identification can also be made before the hair has formed by microscopic examination of characteristic, different hair follicles (1). The homozygous mouse for the sa gene (+sa/+sa) was used as the normal control in this study since there is no evidence that the sa gene causes any defects similar to that of the ch gene (1, 7). The homozygous recessive mice (ch+/ch+) are hydrocephalic from the 11th gestational day, making their identification possible by visual inspection fetally and natally (7). These mice die at birth or a few minutes after birth (1, 7).

The three types of mice described previously were studied at three stages of development: prenatal (15–18 day-old embryos), newborn (19–21 days gestation), and postnatal (10–14 days), with the exception of the homozygous recessive mice (ch+/ch+), which die at birth. The embryonic mice were removed by cesarean section. With the

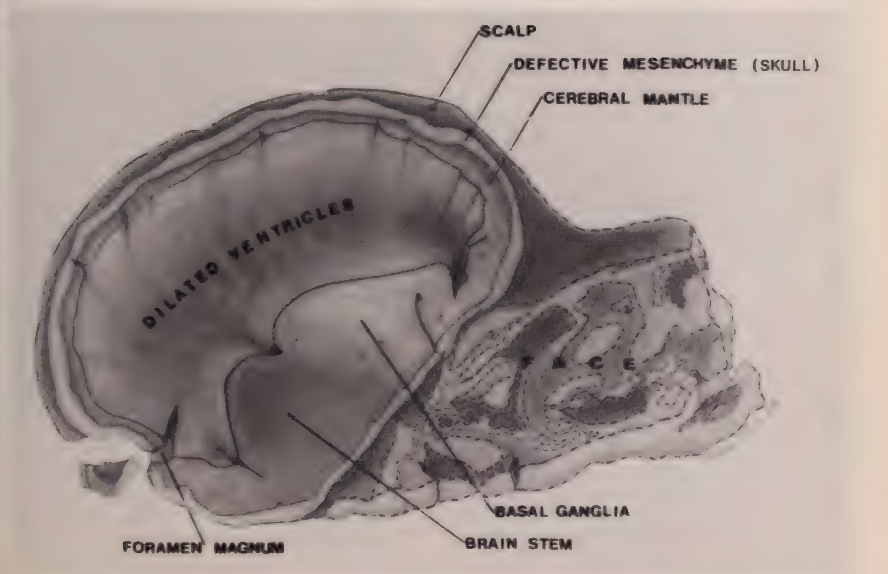


FIG. 1. Drawing of saggital section of ch murine head showing abnormal, narrowed foramen magnum and enormously dilated lateral ventricular system (hydrocephalus). Scale: 10× normal, slightly reduced.

aid of a dissecting microscope, the sternocostal cartilage was excised from the xiphoid process up to and excluding the manubrium. The kidneys were also removed with the aid of a dissecting microscope. Alternate sections of both tissues were stained with hematoxylin and eosin and Masson's trichrome stain, respectively.

The sternal and renal tissue specimens from all three age groups were removed with the aid of a dissecting microscope; fixed in 2% aqueous glutaraldehyde, followed by fixing in phosphate-buffered 1% osmium tetraoxide; dehydrated; and then embedded in Araldite 502. After microscopic identification with methylene or toluidine blue staining, the sections were cut on a Porter-Blume ultramicrotome and placed on grids. The sections were stained with 3% uranyl acetate and counterstained with lead citrate, washed with distilled water, and then examined in a Hitachi 12 electron microscope.

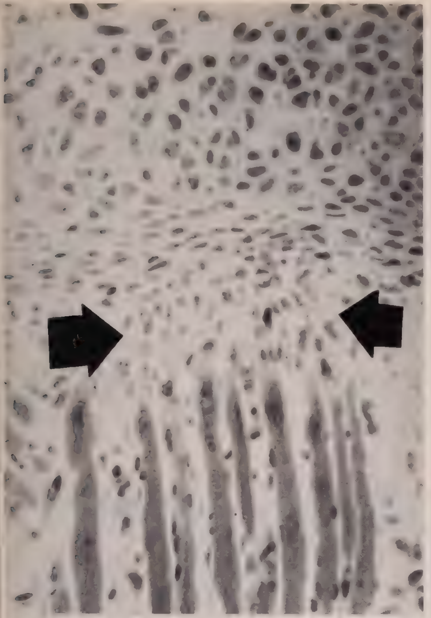
For 15 randomly selected ch fetal and newborn mice and ten satin fetal and postnatal mice, the diameters of both sternal collagen fibrils and proteoglycan granules were measured with electron micrographs using a millimeter scale in a magnifying glass.

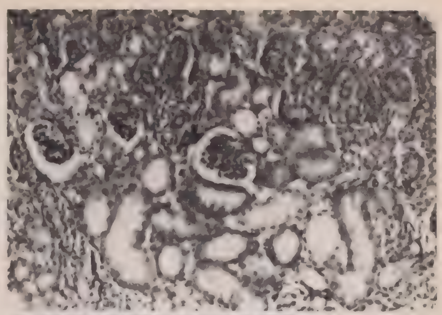
Results

Microscopic Anatomy. Microscopic examination of the sternocostal cartilages of the prenatal, natal, and postnatal mice showed cartilage formation in the center of the sternum of both the normal satin control mice and the heterozygote mice, while cartilage was absent in the homozygote recessive mice. In its place, in the ch mouse, there were fibroblastic-appearing, spindle-shaped undifferentiated mesenchymal cells (Fig. 2). The natal and prenatal ch recessive mouse also had costal cartilages with undifferentiated mesenchymal cells and occasional cartilage cells in the adjacent sternal matrix. The ch sternal region was generally less than one-half the size of the corresponding area in the normal satin and the heterozygote mice, as well as having a different morphologic configuration. The undifferentiated mesenchymal cells of the ch mice, in the area corresponding to the sternal matrix between the costal cartilages, stained poorly, except for an occasional cartilage cell and occasional differentiated striated-muscle cells (Fig. 2). Postnatal normal satin and heterozygous mice developed six ossification centers in the sternum, while the recessive ch mouse developed none. Mineralization was more advanced in the postnatal satin sternum, with a delay of about one to two weeks in the corresponding heterozygote sternum.

Congenital anomalies of the renal system were observed grossly in approximately 71% of the prenatal ch mice and 57% of the natal ch mice. Microscopic examination of ten kidneys of ch hydrocephalic mice revealed abnormalities in all ten, but to a variable degree, while examination of 8 kidneys from satin mice disclosed basically no abnormalities (Fig. 3, 4). All ten ch kidneys demonstrated poor development or immaturity, variable amounts of cellular disorganization, and variable findings of renal dysplasia (Fig. 5). The glomeruli in eight out of ten fetal and natal ch kidneys were more poorly developed and less numerous than the glomeruli of the fetal and natal satin kidneys. These eight kidneys of ch hydrocephalic mice also demonstrated a poorly developed and less advanced tubular system than the age-matched kidneys of satin mice (Fig. 3 and 5). All of these ch kidneys contained abnormally large, primitive, dilated ducts that were surrounded to some extent by a variable cellular mesenchyme in no apparent structural organization (Fig. 5). In the normal kidneys, when mesenchymal elements were present, they appeared to be organizing in future papillary regions (Fig. 3). In the kidneys of the ch hydrocephalic mice, there was no development of an advanced tubular epithelium, as there was in the murine kidneys of satins. Two fetal ch kidneys disclosed no evidence of renal cytoarchitecture, except for a reniform shape macroscopically, and a primitive attempt at tubular organization (Fig. 4). These two ch kidneys contained numerous spindle-shaped or fibroblastic-appearing cells in complete cellular disarray with no definite renal cytoarchitecture, and these concentric bands and arrays of undifferentiating mesenchymal cells were associated with definitive mineral (calcium) concretions (Fig. 4). The other eight ch kidneys, which contained variable numbers of very dilated, primitive ducts, were not found to possess these concretions, but they occasionally had smooth-muscle and cartilage cells in the surrounding cellular mesenchyme.

Ultrastructural Anatomy. In the normal homozygote (+sa/+sa) mouse and in the heterozygote (ch+/+sa) mouse, the plasma membrane of chondrocytes was irregular, scalloped or ruffled, and invaginated. In the hypertrophic region of the sternal matrix, cartilage cells were surrounded by pericellular lacunae containing many electron-dense granules (Fig. 6). These chondrocytes contained an abundance of rough, endoplasmic reticula, mitochondria, and some smooth endoplasmic reticula, Golgi complexes, vacuoles, membrane-bound granular vesicles, glycogen, and lyzosomes (Fig. 7). The intercellular matrix





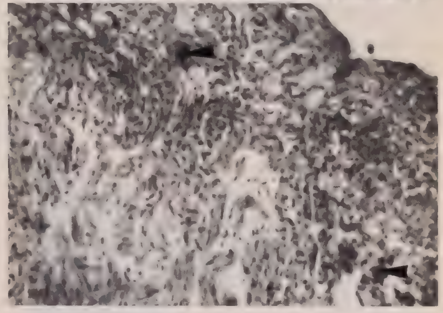


FIG. 2. **Left** Undifferentiated mesenchymal cells (arrows) in sternal region of a developing, newborn ch mouse. The cells arise from peripheral resting zone of hyaline, costal cartilage above, and differentiated striated muscle cells below (toluidine blue ×400, original magnification).

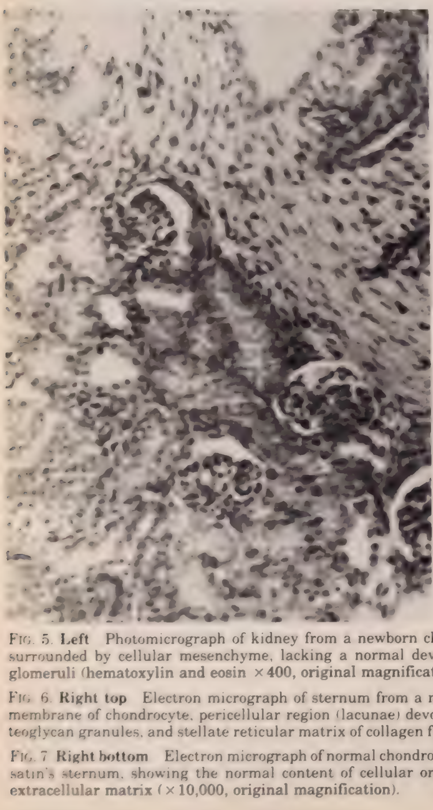
FIG. 3. **Right top** Photomicrograph of developing tubular system with normal immature glomeruli in fetal satin kidney (hematoxylin and eosin ×400, original magnification).

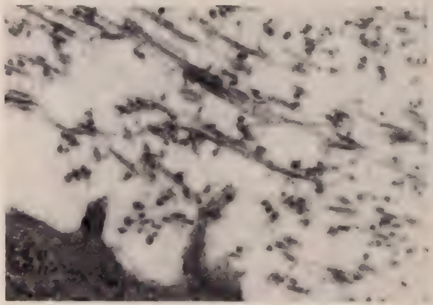
FIG. 4. **Right bottom** Photomicrograph of fetal ch kidney revealing bundles of spindle-shaped undifferentiated mesenchymal cells, completely disorganized and unable to form normal renal cytoarchitecture, but attempting to form tubules (hematoxylin and eosin ×200, original magnification).

of the hyaline cartilage of the sternocostal region contained randomly dispersed numerous collagen fibrils in a fine, feltlike meshwork, interspersed with abundant electron-dense granules. At higher magnification, the electron-dense granules were attached to collagen fibrils or aggregated in the interfibrillar stellate reticulum (Fig. 8). The extracellular matrix of the sternocostal hyaline cartilage showed both granular and fibrillary structures in a regular feltlike pattern. The fibrillary structures were thin collagen fibrils, varying from 10 nm to less than 20 nm in diameter. The matrix granules were rounded or polygonal, varied from 8 nm to 18 nm in diameter, and had a high electron density. Many of these extracellular granules can be shown to be attached tangentially to collagen fibers, or to other granules, to form a coalescent granular structure. The collagen fibers were also found in an arborizing pattern linked to other collagen fibers, or to other granular substances, not only in fetal and newborn satin animals but also in the heterozygote fetal and newborn animals (Fig. 8). In the sternal cartilage of postnatal satin mice, significant mineralization was frequently seen, and numerous vacuoles were found in the chondrocytes in the hypertrophic zone. Ultrastructural examination of several fetal and natal satin-mouse kidneys revealed no vacuolar accumulation of substances.

The homozygote hydrocephalic mice (ch+/ch+) never displayed ossification in the developing sternal regions. In addition, normal chondrification could not be substantiated in the sternal matrix. The intracellular compartment and the intercellular matrix of the fetal and newborn ch hydrocephalic mouse were completely different in ultrastructural appearance in comparison with the respective age-grouped mice of the other two genotypes. Ultrastructurally, the fetal ch hydrocephalic mouse displayed generally much less collagen in both the peripheral and central extracellular compartments, and, moreover, a paucity of extracellular electron-dense granules, which were also viewed in unstained sections. At the periphery of the developing ch sternum, the cells were spindle-shaped or elongated and irregularly shaped, and they appeared fibroblastic (Fig. 10). The peripheral intercellular region contained few collagen fibers and electron-dense granules. In the central region of the developing ch sternum, actual chondrocytes never develop. The sternal mesenchymal cells of both the fetal and newborn ch mice have a nonreticulated or less-scalloped plasma membrane. The cytoplasm contained mitochondria, ribosomes, and rough endoplasmic reticulum, but few lyzosomes and vacuoles and no real Golgi apparatus or glycogen (Fig. 11). The central intercellular matrix contained a paucity of the electron-dense granules and comparatively few collagen fibrils, usually in specific areas and usually having a thicker than normal diameter of 20 to over 80 nm (Fig. 9). At higher magnifications, the collagen fibrils were aggregated in clumps or parallel arrays (Fig. 12), and occasionally some collagen fibrils adjoined to each other to form abnormally enlarged collagen fibrils, some similar to the native collagen of the other connective tissues and having a diameter of 50 nm to more than 80 nm. The diameter of the electron-dense granules varied from 9 nm to 27 nm and appeared slightly larger than the intercellular matrix granules of the other genotypes.

Ultrastructural investigation of the dense regions of spindle-shaped (undifferentiated mesenchymal) cells in the kidneys of the fetal and natal ch hydrocephalic mice revealed cells similar to fibroblasts and structurally resembling renal mesangial cells (Fig. 13). Besides being more numerous and more pronounced than similar cells





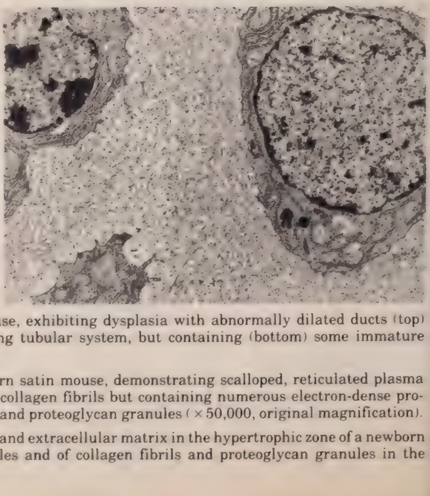
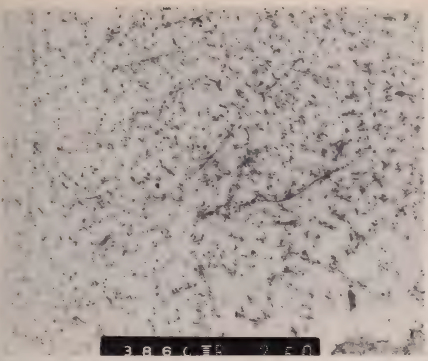


FIG. 5. **Left** Photomicrograph of kidney from a newborn ch mouse, exhibiting dysplasia with abnormally dilated ducts (top) surrounded by cellular mesenchyme, lacking a normal developing tubular system, but containing (bottom) some immature glomeruli (hematoxylin and eosin ×400, original magnification).

FIG. 6. **Right top** Electron micrograph of sternum from a newborn satin mouse, demonstrating scalloped, reticulated plasma membrane of chondrocyte, pericellular region (lacunae) devoid of collagen fibrils but containing numerous electron-dense proteoglycan granules, and stellate reticular matrix of collagen fibrils and proteoglycan granules (×50,000, original magnification).

FIG. 7. **Right bottom** Electron micrograph of normal chondrocytes and extracellular matrix in the hypertrophic zone of a newborn satin's sternum, showing the normal content of cellular organelles and of collagen fibrils and proteoglycan granules in the extracellular matrix (×10,000, original magnification).



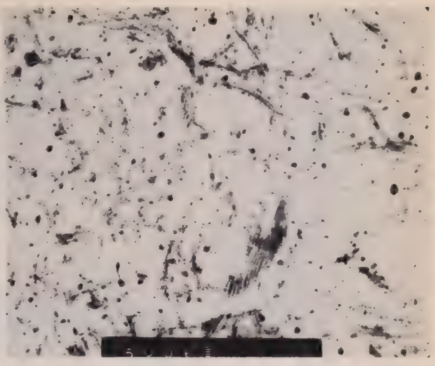


FIG. 8. **Left** Electron micrograph of extracellular matrix of sternum of normal newborn satin mouse, demonstrating regular, arborizing pattern of collagen fibrils, aggregating normally in meshwork containing interfibrillar stellate reticulum of electron-dense proteoglycan granules (×25,000, original magnification).

FIG. 9. **Right** Electron micrograph of extracellular matrix of unformed ch sternal region, from a newborn, disclosing paucity of electron-dense proteoglycan granules and collagen fibrils (×25,000, original magnification).

of normal murine kidneys, these mesenchymal cells were sometimes found in association with tubular epithelial cells. The intercellular matrix also occasionally demonstrated diffuse, randomly oriented bundles of collagen fibers, but frequently there was a lack of matrix materials (Fig. 13). No evidence of accumulation of degradation products or an abnormal deposit of substances in intercellular vacuoles or vesicles was found.

Discussion

To review the history of relevant research findings, multiple skeletal defects have been associated with the recessive ch gene involving the skull, cervical vertebrae, sternum, trachea, and laryngeal cartilages (5, 6); and ch mice die at birth, or shortly after, as a result of asphyxia (1, 5–7). In 1943, Grüneberg investigated the severe congenital hydrocephalus of the ch mouse, which was frequently associated with the intraventricular hemorrhage secondary to rupture of the dural venous sinuses (5). In 1970, Green investigated the abnormal cartilage and demonstrated excess mesonephric tubules associated with severe urogenital anomalies, deficient celiac ganglion cells, and failure of development of the cerebral subarachnoid space around the eleventh day of gestation, paralleling development of a communicating type of hydrocephalus in the ch mouse (7). In 1973, Raimondi substantiated the markedly compressed cerebral mantle secondary to the hydrocephalus, as well as a markedly compressed spinal parenchyma secondary to hydromyelia (8).

The failure of multiple skeletal structures to develop appeared to correlate with a failure of systemic endochondral ossification, except in the skull, which mainly develops by membranous ossification (4). The failure of membranous bone development of the ch skull is most likely caused by a pressure necrosis from the underlying, severe, congenital hydrocephalus (4). The murine sternum normally develops from two longitudinal plates of mesoderm (9, 10). The mesodermal sternal bars subsequently undergo chondrification, migrate toward the midventral line, and fuse with each other in a rostral to caudal direction (9, 10). In normal mice, the median hyaline cartilaginous plate later undergoes ossification to form six sternal centers located between the attached ribs (10). In the recessive ch hydrocephalus mouse, Green, in 1970, found an absence of segments constituting the body of the sternum; in other instances she found that the costal cartilages were continuous from one side to the other across the midline, and that the manubrium and xiphoid process were commonly abnormally shaped or fragmented (7). Green rarely found skeletal abnormalities in heterozygotes because a recessively inherited biochemical effect is not usually expressed morphologically in heterozygotes (7). Breen and Richardson, in 1973, quantified the acidic glycosaminoglycan concentration in developing sternocostal cartilages of the recessive ch mouse, the normal satin mouse, and the heterozygote (1). They found that the defective sternocostal cartilage in the recessive ch animal at prenatal and natal ages had a threefold reduc-

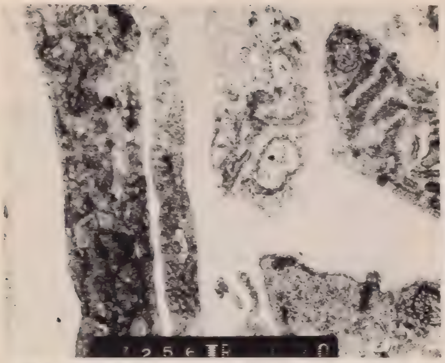


FIG. 10. **Left** Electron micrograph of undifferentiated mesenchymal cells in resting zone of sternal region of a newborn mouse, revealing few intercellular collagen fibrils and proteoglycan granules (× 12,000, original magnification).

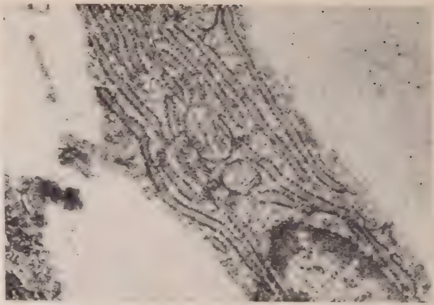


FIG. 11. **Right** Electron micrograph of spindle-shaped (fibroblastic) mesenchymal cell in sternal matrix of a newborn ch mouse, demonstrating smooth plasma membrane, well-developed endoplasmic reticula with polyribosomes, mitochondria, but no Golgi complex, and pericellular space devoid of granules and fibrils (× 25,000, original magnification).

tion in acidic glycosaminoglycan (proteoglycan) concentration, mainly in chondroitin sulfate (1). The failure of sternal development in the ch animal coincided with diminished fluorescence with acridine orange staining, or a decreased number of available polyanionic binding sites (1). On microscopic examination, Breen and Richardson also identified an absence or paucity of normal-appearing chondrocytes with replacement by fibroblastic-appearing, undifferentiated mesenchymal cells (1). They also found that the heterozygote (ch+/+sa) had a greater chondroitin sulfate concentration than the normal satin mouse at the same age, which was thought to be the result of a microscopic delay of sternal ossification (1).

Ultrastructural examination revealed a similar appearance of the cartilage cells in the developing sternocostal cartilages of both the normal satin and the heterozygote mice, except for the delay in mineralization of the heterozygote. The intercellular matrices of the cartilage of both genotypes appeared similar in both the content and form of the small-fibril collagen and the electron-dense granules (the proteoglycans), which are associated with and adjacent to the collagen fibrils in the interfibrillar matrix. Serafini-Fracassini and Smith, in 1974, and others have stated that both are synthesized and secreted into the intercellular matrix by the differentiated chondrocytes (11–13). In the sternal regions of fetal and newborn ch mice, the fibroblastic-appearing mesen-

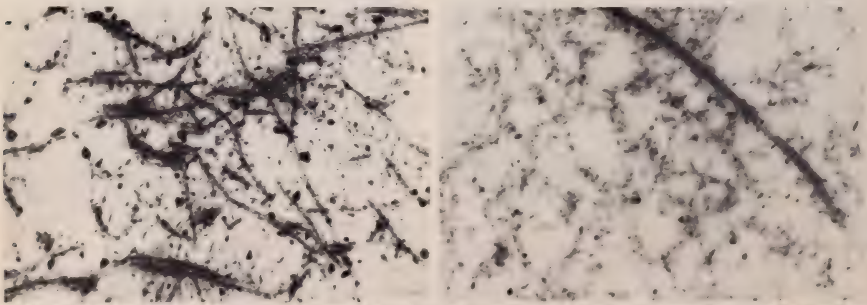


FIG. 12 Electron micrographs of extracellular matrices from two different abnormal, nonformed, sternal regions of ch newborns, disclosing fewer but somewhat enlarged, electron-dense proteoglycan granules, and collagen fibrils organized into abnormal clumps (**left**) or aggregated into thicker diameter of collagen (**right**), similar to native collagen (× 40,000, original magnification).

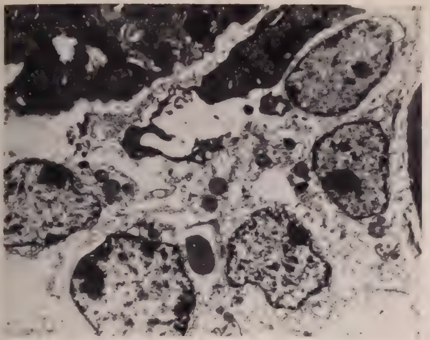


FIG. 13. Electron micrograph of a fetal ch kidney revealing nuclei with perikarya of multiple spindle-shaped mesenchymal cells (mesangial cells) and with intercellular space almost completely devoid of proteoglycan granules and collagen fibrils (×4,000, original magnification).

chymal cells, having a less scalloped cell membrane, are associated with a paucity of electron-dense granules with abnormal aggregates or clumps, and sometimes abnormally large, native-like collagen fibrils in the intercellular matrix. These findings resemble others developed in studies of a genetic strain of mice with chondrodysplasia (14, 15).

Glenister, in 1976, defined a chondrocyte as a cell that synthesizes large quantities of chondroitin-sulfate proteoglycan and a tropocollagen molecule into the extracellular matrix (16). Levitt and Dorfman, in 1974, showed experimentally that blocking the synthesis of the chondroitin-sulfate proteoglycan due to insufficient intracellular Golgi complexes leads to failure of mesenchymal cell differentiation into cartilage cells. Without chondrocytes and sufficient chondroitin-sulfate proteoglycans, ossification cannot occur (17). While the sternocostal chondrocytes of our normal satin and heterozygote mice produced sufficient amounts of chondroitin-sulfate proteoglycan and possessed the normal cellular organelles, the recessive ch hydrocephalic mouse contained cells in the sternal region having mitochondria, endoplasmic reticula, and polyribosomes, but no real Golgi complexes (Fig. 11). In addition, the undifferentiated mesenchymal cells of the fetal and newborn ch sterna produced much less chondroitin-sulfate proteoglycan and had fewer extracellular polyanionic binding sites available. Therefore, the extracellular collagen fibrils aggregated, or clumped abnormally, or bound abnormally to form larger collagen fibers because of a deficiency of polyanionic binding sites (Figs. 8, 12).

With congenital genetic disorders with multisystem involvement and multiorgan anomalies, such as the proteoglycan (mucopolysaccharide) disorders, there is usually an interrelationship among abnormalities of the central nervous, musculoskeletal, cutaneous, and urogenital systems (4). Green demonstrated that the ch hydrocephalic mice not only had defective endochondral ossification, but also had abnormalities of the urogenital system including double ureters, hydronephrosis, and hydroureter on one or both sides (7). She found that ch kidneys frequently appeared larger than normal, or were really double kidneys, instead of the normal murine unilobar kidney (4, 7). The ch animals were most commonly found to have an extra ureter on one or both sides, the extra ureter usually forming an extra renal pelvis but frequently ending blindly (7). Therefore, many of these kidneys were probably nonfunctional. Green traced the urogenital defect in fetal animals to the formation of excess mesonephric tubules filling the whole region between the normal mesonephros and the kidney, which was also responsible for a reduction of coeliac ganglion cells (7). Green hypothesized that in the ch mice a defect in the mesenchyme slowed or delayed migration of cells, thereby promoting an aggregation of mesenchymal cells (7). Anatomic variations in the renal system of the hydrocephalic ch murine strain could be explained on the basis of differential penetrance of the ch gene and variable physical expression. Our findings in the ch renal system indicate that renal dysplasis and disorganization appear to be the basic cellular defects, occurring from a primary failure of mesenchymal differentiation.

Renal Dysplasia. Renal dysplasia is associated with anomalies of the lower urinary tract, secondary hydronephrosis and hydroureter, genital anomalies, and abnormalities of other organ systems, including the cutaneous, central nervous, and musculoskeletal systems (18, 19). It is specifically a failure of metanephric differentiation resulting in disorganization of the renal parenchyma, the formation of immature nephronic and ductal structures, and sometimes in cyst formation (18, 19). While the anatomical size and shape of the kidney can vary depending upon its histological contents, the kidney is physiologically nonfunctional (18, 19). Renal dysplasia is usually associated with immature glomeruli, immature (primitive) and dilated ducts that are surrounded by concentric mantles of cellular mesenchyme, and occasionally with smooth muscle cells, ectopic bars of metaplastic cartilage, and subcapsular concretions (Fig. 5) (18, 19). Our microscopic and ultrastructural findings of cellular immaturity and disorganization, associated with the presence of numerous mesenchymal cells, support the concept of renal dysplasia in the ch renal system, but with a variety of histological abnormalities (Figs. 4, 5, 13). In contrast to human proteoglycan disorders affecting the renal system, no abnormal accretion of proteoglycans was found extracellularly, and no intracellular accumulation of abnormal electron-dense substances or numerous membrane-bound vacuoles were identified in the ch kidneys.

We proposed that the failure of the sternal mesenchymal cells in the hydrocephalic ch mouse to differentiate into chondrocytes, and subsequently to undergo ossification, occurs because of inadequate amounts of the chondroitin-sulfate proteoglycan (1, 4). Because of the absence of membrane-bound accumulated degradation products intracellularly (2, 3), we also proposed that the insufficient production of chondroitin sulfate was due to a genetic synthetic defect that may be intracellular due to defective or absent Golgi complexes (4). Because of the close association and interrelationships among abnormalities in the central nervous, musculoskeletal, and urogenital systems, investigation of the hydrocephalic ch murine model affords a unique opportunity to study the cellular mechanism and molecular basis of a congenital genetic disorder similar to the human proteoglycan disorders, formerly called mucopolysaccharidoses.

Acknowledgments

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Changes in Free Histamine in Peripheral Circulation Following Cockroach-Antigen Challenge in Asthmatics

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Abstract

To determine the relationship between allergic mediators and the response to antigen inhalation in allergic asthmatics, we studied the changes in circulating free histamine levels during an antigenic-inhalation challenge test in 13 cockroach-antigen (CRa) sensitive, chronic perennial asthmatics. Bronchial sensitivity was determined by reduction in forced expiratory volume in one second (FEV_1), FVC, and in maximal midexpiratory flow rate (MMEF) as compared to a control challenge. Serum IgE was assayed, and the CR radioallergosorbent test (RAST) as well as an in vitro anaphylactic leukocyte histamine-release test (HR50), were done. The results revealed that all CRa-sensitive asthmatics have significantly elevated circulating plasma histamine levels immediately following CR antigen inhalation in comparison to the control challenge period ($p < .001$). Elevated histamine levels reached peak levels within five minutes following CRa challenge and remained elevated until isoproterenol inhalation reduced the acute bronchospasm. The bronchial sensitivities of CRa asthmatics correlated inversely with free histamine levels. In vitro assays such as total IgE, CR RAST, and HR50 against CRa poorly reflected the bronchial sensitivities of cockroach-sensitive asthmatics.

The basic pathophysiologic abnormalities leading to development of bronchial asthma are complex, especially for chronic perennial asthma. This form of asthma is usually severe, hard to control, and frequently becomes worse, so that asthmatics may be incapacitated throughout their lives. For these asthmatics, the role of inhalant allergens, and consequently the role of antigen-induced anaphylactic mediators, has still not been clearly demonstrated (1, 2).

Lately, cockroach-antigen (CRa) sensitivity has been reported to be very high in severely asthmatic populations (3, 4). It is also known that CRa inhalation induces an immediate or late asthmatic reaction in cockroach-sensitive asthmatics (5, 6). As part of an on-going study for understanding cockroach asthma among the chronic asthmatic population, we measured the changes in circulating free histamine levels following CRa challenge in cockroach-sensitive chronic asthmatics. We have investigated the relationship between their bronchial sensitivity to the antigen and its antigen-induced anaphylactic mediator in the peripheral circulation. Sensitivity of the basophil-rich leukocytes was also studied in relation to bronchial sensitivity in the same population.

Subjects and Methods

Thirteen chronic asthmatic subjects, aged 13 to 64 years, participated in the study after giving informed consent. All have had perennial bronchial asthma of moderate severity by the criteria described by Reed and Townley (1). In order to maintain daily activity without having asthmatic

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attacks, the subjects had been required to use regular "round the clock" bronchodilators for at least three years. Subjects who required corticosteroid therapy and those who had received previous immunotherapy were excluded from the study. The average duration of our subjects' asthma was 16.5 years (3–36 years). The cockroach sensitivity of these asthmatics was determined by the previously described criteria (4). All but one had four to twelve positive reactions to 25 common inhalant allergens tested, in addition to sensitivity to CR antigen. Serum IgE and CR radioallergosorbent (RAST) were measured as previously described (6, 7). CR RAST (%) was expressed as percentage uptake of pooled control sera against CR antigen.

Bronchial Provocation Testing (BPT). Subjects studied were free of an acute attack of asthma for at least one week prior to testing. All bronchodilators and antihistaminic drugs were withheld for at least 10–12 hours. BPT was carried out by the modified method, as previously described (4, 6), by measuring the reduction in forced expiratory volume in one second (FEV_1), FVC, and maximal midexpiratory flow rate (MMEF), using a volumetric spirometer (VS-400) attached with a volumetric processor (VS-800, Puritan Bennett, Woburn, Mass). When the subject's FEV_1 was below 70% of its predicted value or the substance used as a control challenge induced nonspecific bronchospasm (Δ $FEV_1 \geqq 15\%$), the subject was excluded from the study. A buffered saline diluent of the CRa was used in the control challenge which was carried out on every subject prior to the CRa challenge. Pulmonary functions were measured at 0, 5, 10, and 15 minutes after a control challenge; at 0, 5, 10, 15, 20, and 25 minutes following a CR challenge; and at 5 minutes after isoproterenol inhalations. BPT with CRa antigen was considered positive when FEV_1 was reduced 15% or more from the baseline value.

Blood Sampling and Plasma Histamine Assay. Prior to BPT, an antecubital vein was cannulated with a No. 19 scalp vein needle with a heparin lock. Blood samples were drawn at 0, 5, 10, and 15 minutes after the control challenge; at 1, 5, 10, 15, 20, and 25 minutes after the CRa challenge; and during the recovery period following isoproternol inhalation. Three milliliters of heparized blood were drawn into a plastic syringe, then immediately placed in icewater. Plasma was then separated and stored at −70°C. until assayed for free histamine.

Plasma histamine was measured by an enzymatic isotopic technique as described by Shaff and Beaven (8). This method involves conversion of free histamine in the plasma sample to ^{14}C-methyl histamine by incubation with s-adenosylmethionine (^{14}C-methyl) and histamine-N-methyl-transferase prepared from rat kidney. A small amount of ^{3}H-histamine was mixed with plasma samples to monitor recovery. The ^{14}C-methyl histamine was isolated by extraction into chloroform and assayed for radioactivity by scintillation counting (Model 3320, Packard, Chicago, Ill). The amounts of free histamine in plasma samples were calculated from a standard curve prepared in plasma. All specimens were assayed in duplicate.

Leukocyte Sensitivity Test. Leukocyte sensitivity to CRa was measured, in vitro, by an anaphylactic histamine-release assay using the method described by May et al (9). Basophil-rich leukocytes (3×10^6 cells/ml) were collected from the asthmatic subjects, washed three times, and resuspended in Tris ACM buffer (Fisher Scientific Co., Fairlane, NJ). The crude CRa mixed in equal parts from three different species (Lot R8639, R8640, R8641) in serial dilutions, was added to the leukocyte suspensions in the presence of normal pooled human sera. The released histamine was measured fluorometrically by a spectrofluorophotometer (American Instrument Co., Silversprings, Md). The amount of CRa (μg/ml) required to induce a 50% histamine release (HR) from the total histamine present in the leukocytes was designated as HR50 and as the cutoff point for leukocyte sensitivity to the CR antigen. Lyophilized cockroach antigen (whole body) was provided by Hollister-Stier Co. (Spokane, Wash).

Statistical Analysis. The data presented are in the form of the mean ± SE, and significance was analyzed by the Student *t* test and paired Student *t* test.

Results

Cockroach-sensitive asthmatics characteristically show positive reactions to multiple inhalant allergens in addition to CR antigen (this was true of 12 of our 13 subjects), with fluctuating asthmatic symptoms throughout the year. One half of the subjects studied had chronic rhinitis or sinusitis in addition to bronchial asthma which required numerous visits to emergency rooms and hospitalizations. All but one patient (No. 4, IgE 29 IU/ml) had elevated total IgE levels (737 ± 180 IU/ml). One half of those studied showed negative CR RAST results, in spite of their strong positive reactions to CRa as measured by allergy skin-testing and elevated IgE levels.

TABLE 1

Changes in Plasma Histamine Level, FEV_1, and MMEF after CRa Challenge on 13 CR Asthmatics

Time min (n)	Histamine (ng/ml)	FEV_1 % change (Mean ± SE)	MMEF % change
Control			
5	0.5 ± 0.1	+0.6 ± 2.1	+0.23 ± 3.7
10 (7/13)	0.6 ± 0.2	+2.0 ± 2.5	+0.53 ± 4.4
15 (7/13)	0.3 ± 0.2	−1.4 ± 2.6	−7.91 ± 3.7
CR antigen			
5	11.8 ± 1.7*	−38.8 ± 6.7*	−40.5 ± 4.6*
10 (12/13)	8.6 ± 1.6*	−36.3 ± 5.4*	−45.9 ± 5.3*
15 (7/13)	7.5 ± 1.0†	−38.0 ± 7.3*	−54.0 ± 7.2*
20 (5/13)	9.0 ± 1.6*	−33.7 ± 5.7*	−46.3 ± 6.5*
25 (5/13)	6.7 ± 2.2†	−32.7 ± 7.0*	−48.2 ± 11.6*
Isoproterenol			
5	3.7 ± 0.7	−27.4 ± 5.1	−28.8 ± 15.6†

+: increase −: decrease

* $p < 0.001$

† $p < 0.01$

Bronchial Provocation Test and Plasma Histamine. Table 1 and Figure 1 summarize the changes in plasma histamine levels and in pulmonary function following diluent and CR challenges and after isoproterenol inhalations. Plasma histamine levels rose significantly following the CRa challenge from those observed during the control-challenge period ($P < .001$). The histamine levels remained elevated throughout the observed period (30–50 minutes) until reduced by isoproterenol intervention (but the levels did not return to the respective prechallenge levels). The reductions in FEV_1, MMEF, and FVC following CRa challenge were also significant ($P < .001$) in comparison to the control-challenge period. These changes in lung function and plasma histamine levels induced by the CRa challenge were simultaneous, instantaneous, and inversely correlated ($r = 0.91$). The induced changes were sustained during the period of observation until isoproterenol intervention reversed the asthmatic reaction as quickly as it had been induced.

Following the challenge with 400 PNU of the CRa, the majority of the studied subjects (11/13) showed moderate to severe clinical asthma with coughing and wheezing. However, two (Nos. 4, 6) who had moderate perennial asthma with rhinitis showed mild auscultatory wheezing upon 1200 PNU of CRa inhalation (Table 2). Subject 13 had the most severe immediate asthmatic reaction following 400 PNU of the CRa, with diaphoresis and respiratory distress; therefore she received isoproterenol inhalation three minutes after the antigen challenge, and another three minutes had passed when blood for plasma histamine was drawn. Her Δ FEV_1 of 53% was the value obtained prior to isoproterenol treatment. Isoproterenol (1:200, 3 inhalations) caused a reduction in plasma histamine levels and improved lung function in all tested asthmatics. Clinically the asthmatic distress disappeared. Yet in asthmatics responding severely to the CR challenge (8/13), neither their plasma histamine levels nor their lung functions reversed completely to control-challenge levels (Table 1). The CR negative allergic asthmatics who had perennial symptoms did not show any elevation of histamine levels or any reduction in lung function following the CRa challenge.

Leukocyte Sensitivities. Anaphylactic leukocyte sensitivity of the cockroach-sensitive asthmatics was measured in 11 of the 13 subjects studied. All tested showed extreme sensitivity toward CRa challenge (mean HR50: 2.9 × 10^{-5} μg/ml—Table 2). The leukocyte sensitivity, however, was not correlated with CR RAST or with their IgE levels. Leukocyte sensitivity also did not reflect the elevated plasma histamine levels following BPT or the individual's bronchial sensitivity ($r = 0.61$, $r = 0.56$). The HR50, however, was universally increased when the same leuko-

TABLE 2

Comparison of CR RAST and Leukocyte Sensitivity to CR, and Changes in Histamine and FEV_1 Following CR Challenge

			Change at 5 min after CR challenge	
Pt. No.	CR RAST (%)	HR_{50} (μg/ml)	Plasma histamine (ng/ml)	Decrease FEV_1 (%)
1	754	9.5 × 10^{-7}	7.5	33
2	ND	ND	14.0	48
3	929	6.0 × 10^{-5}	15.5	53
4	122	4.0 × 10^{-7}	1.2 (10.)*	3(23)*
5	367	1.0 × 10^{-5}	6.6	17
6	184	3.5 × 10^{-5}	0.9 (6.1)*	6 (18)*
7	166	ND	13.1	26
8	ND	2.5 × 10^{-5}	15.6	52
9	462	4.0 × 10^{-4}	15.6	41
10	2539	2.0 × 10^{-6}	18.8	58
11	1043	9.0 × 10^{-5}	6.6	35
12	ND	7.5 × 10^{-6}	13.1	41
13	ND	5.0 × 10^{-7}	7.2	53
Mean ± SEM	739 ± 268	2.9 ± 0.9 × 10^{-5}	11.8 ± 1.7	38.7 ± 6.7

ND: Not done.

HR_{50}: The amount of CR to induce 50% of total histamine release from basophil-rich leukocytes (3 × 10^6 cells/ml).

* Values following 15 inhalations of CR (1200 PNU).

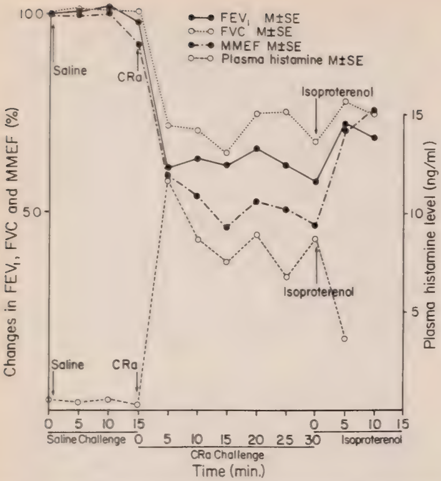

FIG. 1. Mean changes of histamine levels following challenges by saline control and cockroach (CR) antigen and after isoproternol inhalation. CRa ↓ indicates time of cockroach antigen inhalation.

cytes were resuspended in autologous serum as compared to suspension in control pooled serum or nonallergic asthmatic serum. This result is similar to what we found in our previous study on cockroach asthmatics (10).

Discussion

Data in this study demonstrated that bronchial provocation testing with CRa induced an immediate rise in plasma histamine in the peripheral blood, which correlated inversely with reduced lung function in cockroach asthmatics. A similar finding has been reported for asthmatics sensitive to grass and ragweed pollen (11) as well as for asthmatics tested following house-dust mite (*D. pteronyssinus*) challenge (12). Atkins et al (11) reported that elevated histamine level occurred within two minutes following high-dose ragweed-antigen challenge in seasonal asthmatics. Yet their report showed some wide fluctuations in individual histamine levels after the antigen challenge, such as 80 ng/ml in two minutes and 7 ng/ml in 5 minutes in the same subject. However, Brown et al (13), using a novel double-isotope technique, reported that peak plasma histamine was noted at 10 minutes after antigen challenge (*D. farinae* and mixed grass) in five asthmatic subjects. Their average peak plasma histamine level was 0.25 ng/ml.

Kaufman et al (12) found that challenge by house-dust mite (*D. pteronyssinus*) induced elevated histamine levels during immediate and late asthmatic reactions and that the plasma histamine elevation was blocked by premedication with disodium cromoglycate. Not only plasma histamine but also neutrophil-chemotactic-factor (NCF) elevations were observed following the appropriate antigen challenge in grass- or ragweed-sensitive asthmatic subjects by Martin et al (14). The mast cell mediator(s) have been detected in nonimmunologically induced bronchospasm, such as methacholine inhalation (11) and acetyl salicylic acid challenge (15). Lee et al (16) reported that exercise-induced asthma also produced elevated plasma histamine and NCF activity among their allergic asthmatic subjects. They found a significant correlation between concentrations of histamine and NCF and the magnitude of air flow obstruction after exercise as well as after the antigen challenge.

These findings suggest that the additional plasma histamine in the peripheral circulation is one of the liberated mediators from mast cells in the lung compartment. Recently, Allen et al (17) reported that arterial histamine levels rose, but not venous plasma histamine, following inhalation of a high concentration of cat antigen by subjects with cat-induced asthma. It is also known that intravenously infused histamine given in sufficiently large amounts may induce bronchospasm in asthmatics, usually accompanied by systemic effects such as flushed face and headache (18, 19). Therefore, in our study, the high levels of venous histamine in the absence of systemic effects indicate that locally liberated mast-cell mediators may have been extremely high, as the lung function studies suggest.

Though there was a wide individual variation in plasma histamine levels, the majority of studied subjects showed the highest levels within five minutes. The levels remained steady, with a very slow downward tendency. The reduced lung function, however, reached a plateau or deteriorated further during the observed period after CRa challenge (Fig. 1). Further deterioration of lung function with decreasing histamine levels may be due to the effects of secondary mediators such as SRS-A (1, 2). A wide range of histamine levels and disproportionate bronchial sensitivities (Fig. 2) have also been noted (11, 12). These variations may be due to many factors, such as the histamine-assay technique (8, 16, 19), the characteristics of the antigen and the quantity used for challenge, and the hypersensitivity of individual asthmatics to a given antigen. In our study, one of the possible causes for this variation

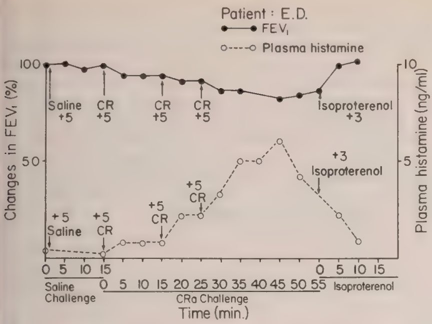

FIG. 2. Changes in histamine levels and lung functions observed in Patient 6, an asthmatic with mild CR sensitivity, following the BPT with CR challenge. Symbol +5 ↓ indicates five vital-capacity-level inhalations of the tested solutions.

may have been the effect of residual medications, such as theophylline or terbutaline, in the plasma, even though medications were withheld for 10–12 hours prior to testing. As Martin et al (14) have described, the effect of these premedications almost completely abolishes the plasma histamine rise as well as the bronchospasm following the antigen challenge. This might also explain the discrepancy between the leukocyte sensitivity of the washed cells and the histamine levels in the plasma of our subject no. 1 (Table 2) following CRa challenge. Further study is warranted to clarify this question.

Unlike histamine levels in experimentally induced asthma, histamine levels in naturally occurring asthmatic attacks have not been well categorized. While Bruce et al (20) reported an elevated whole-blood histamine level during acute asthma, using enzymatic isotopic assay, others (21,22) could not detect free histamine using fluorometric assay during acute asthma. Simon et al (23), however, reported a significant increase in free histamine in the general circulation in asthmatic subjects. Using an isotopic assay or a more sensitive method (8, 19) it was found that severe asthmatics with reduced lung functions more consistently showed elevated free histamine levels than the asymptomatic groups. Yet the severe asthmatic group which Simon et al studied had higher spirometric values than those of our subjects who developed an asthmatic reaction following an antigen challenge (Tables 1 and 2). One of the more severe forms of naturally occurring bronchial asthma is the asthmatic state found in patients seen in emergency rooms of inner-city hospitals. The majority of these patients have more abnormal spirometric values (24, 25) than those seen in our subjects during induced asthma attacks or in those reported by Simon et al. It is therefore conceivable that their plasma histamine levels if measured at the time of an emergency-room visit might be very high, which might give a clue to the severity of their asthmatic state.

Acknowledgments

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Reproducibility of the Red-Cell-Adherence Test: Technical and Practical Considerations

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Abstract

Using the red-cell-adherence (RCA) test to determine the presence of the blood group antigens A, B, and H in tissues, we compared readings of five observers on permanent, stained sections of various organs of 50 patients. All five observers agreed on which blood group antigens were present in the tissues of 45 patients. In the other 5 patients, four observers agreed on 4 patients; only two observers agreed on 1 patient, but the results were reconciled after a second reading. Moreover, results of the RCA test on permanent, stained sections agreed with the results on wet, unstained sections. Our findings indicate that the RCA test is a highly reproducible test for determining blood group antigens A, B, and H in tissues.

The red-cell-adherence (RCA) test is an immunohistochemical test for the presence of blood-group antigens A, B, and H in tissues. The test has been used in our research laboratories to study the development of blood-group antigens in embryos and fetuses (1), their distribution in various organs of human beings (2) and monkeys (3), and their behavior in neoplasms of the oral epithelium (4) and other organs (5). More recently, we have used the RCA test in the clinical laboratory to help in the diagnosis and treatment of patients with cancer of the bladder (6).

The RCA test has already been shown to be reproducible as a technique when an observer or a group of observers reads the same test more than once (5, 6). However, inter-observer reproducibility, that is, how readings of different observers compare, has yet to be studied in the RCA test.

In this report, we present the results of a study of the interobserver reproducibility of the RCA test for determining blood group antigens A, B, and H in tissues.

Materials and Methods

Tissue from various organs of 50 patients with known blood type who had surgery for noncancerous disorders were used in the study. Specimens were fixed in ten percent formalin, cut into blocks, dehydrated in alcohols, embedded in paraffin, cut in serial or step sections at five micrometers, and stained with hematoxylin and eosin. Unstained sections from a representative block were used for the study.

RCA Test. We modified the method for permanent, stained preparations of the RCA test developed in our laboratory (7, 8) as follows: (a) sections were not prestained with hematoxylin; (b) time of incubation with antisera and *Ulex europeus* was shortened to 15 minutes, and washes to 5 minutes, with the use of a staining plate at 37°C; (c) wet, unstained preparations were read, and then the indicator red blood cells were fixed by immersing the slide directly in glutaralde-

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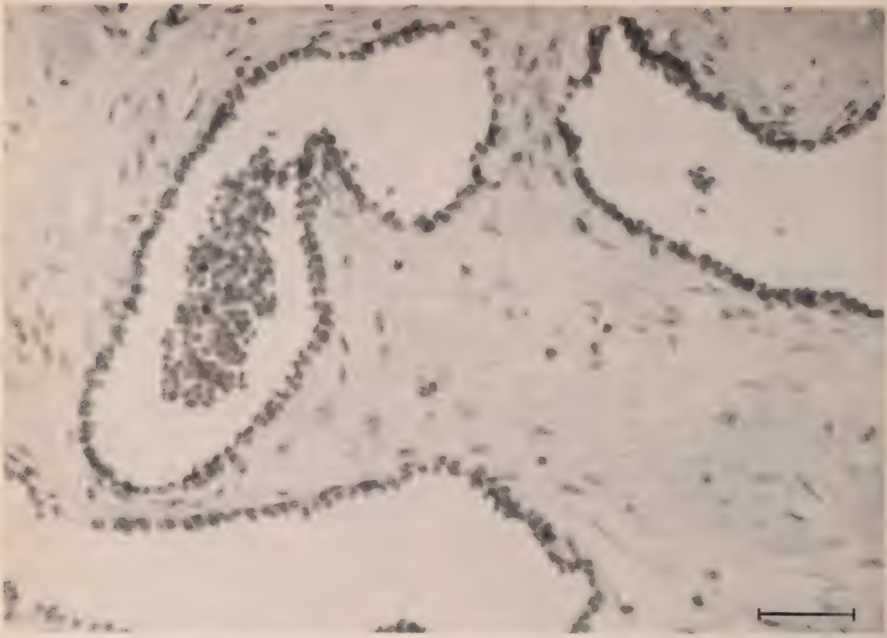

FIG. 1. Permanent, stained preparation of prostate gland showing indicator red blood cells adherent to endothelial cells of blood vessels (bar = 100 μm).

hyde; and (d) sections were stained with hematoxylin and eosin.

The first modification allowed us to read the test on wet, unstained sections where the indicator red blood cells were not fixed or stained and to compare results with the permanent, stained sections. The second modification shortened the test from four hours to 45 minutes.

Reproducibility Experiment. Five observers participated in the experiment. Two observers were experienced in reading the RCA test; the other three were pathologists who had no experience with the test. Each observer at one sitting independently read the permanent, stained slides and recorded results. Results were then tabulated and compared. In cases where the results did not agree, the slides were read again to see if the results could be reconciled. In the second reading, the observers were given several sets of slides to read and were not told in which set, if any, their readings had disagreed with those of the other observers. The reconciled results of the permanent, stained slides were then compared with those of the wet, unstained preparations of all cases read by one of the observers.

Results

Permanent, stained preparations differed only slightly from the wet, unstained preparations (Figs. 1, 2). In both preparations the indicator red blood cells adhered to the tissues, presumably to the binding sites of the antigens with the antibodies or *Ulex europeus*. More of the fixed, stained indicator red blood cells appeared crenated compared to those in the wet, unstained preparations. Also, the indicator red blood cells in the permanent, stained preparations were more deeply stained with eosin and smaller compared to the patients' red blood cells. In contrast, the indicator red blood cells of the wet, unstained preparation appeared larger than those of the patients.

The distribution of the blood-group antigens in the prostate gland, testis, uterine cervix, endometrium, myometrium, ovary, Fallopian tube, vaginal wall, breast, appendix, colon, stomach,

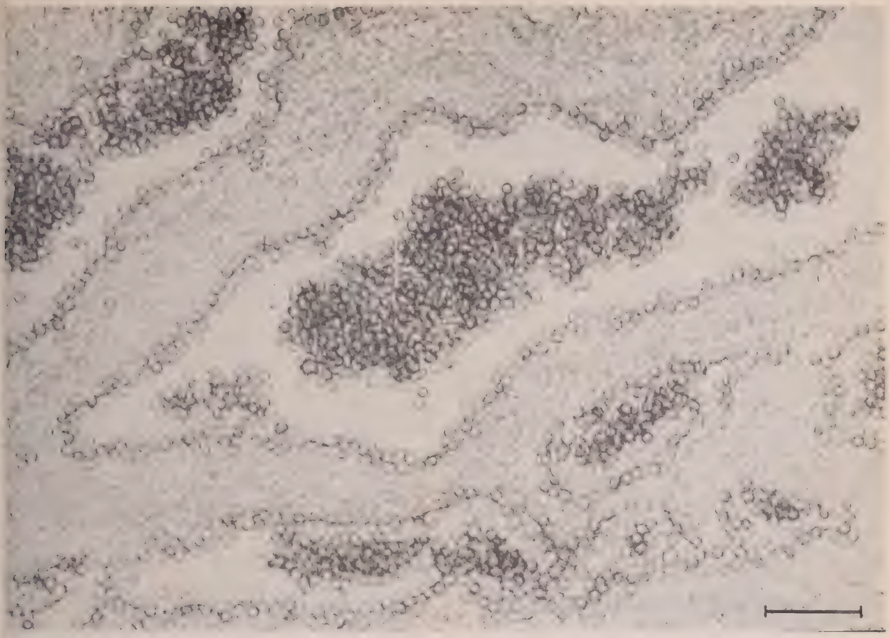

FIG. 2. Unstained wet preparation of same tissue shown in Fig. 1. Indicator red blood cells are larger than patient's red blood cells in lumen (bar = 100 μm).

gall bladder, kidney, lung, lymph node, autonomic ganglion, subcutaneous fat, skin, skeletal muscle, thyroid gland, and placenta of the 50 patients was similar to previous studies (1, 2, 5). Briefly, the endothelial cells of blood vessels were positive in all tissues. In contrast, the connective tissues, fat, and lymph nodes were negative, while the epithelial and other specialized cells were positive in some but not all the organs. We also noted the slight positivity of H antigen in patients with A or B antigen in their tissues.

TABLE

Evaluations of Tissue Blood-Group Antigens in which Observers Disagreed

	Experienced		Inexperienced			
Organ	1	2	3	4	5	(1)*
Placenta	O	O	O	B†	O	(1)
Placenta	A	A	A	A	O†	(A)
Cervix	O	O	O	A†	O	(O)
Fat	AB	AB	B†	AB	AB	(AB)
Endometrium	AB	A†	AB	B†	A†	(AB)

* Reading on wet, unstained sections. All others read on permanent, stained sections.

† Reconciled in second reading.

Reproducibility Experiment. All observers agreed on what blood-group antigen was present in the tissues of 45 patients. In 5 patients, there were disagreements after the first reading but these were reconciled after a second reading. The reconciled results of the permanent, stained slides were identical to the wet, unstained preparations (Table).

Discussion

Our findings show a high interobserver reproducibility of the RCA test for determining blood group antigens A, B, and H in tissues on permanent, stained slides. However, because the wet, unstained preparations are used as quality controls, we recommend use of both preparations, especially in the clinical laboratory where the test can be used in the diagnosis and treatment of patients with cancer (5, 6) or, rarely, in the identification of the blood group of suspected victims of homicides.

We do not know for certain why our readings differed in five patients. Experience could have played a part because the results were reconciled after a second reading. In this latter reading, the less experienced observers focused their attention on the endothelial cells of the blood vessels. They had become more aware that the indicator red blood cells differed from those of the patients. The slight positivity of the H antigen in the epithelial cells of tissues positive for A and B antigens (2) was no longer confusing. It is more difficult to explain, however, how the two experienced observers disagreed on one patient. It may be because the specimen was endometrium, a more difficult tissue to read, or because the patient was a type AB and the B was less strong.

Disagreements could also have resulted from reading the slides as an experimental rather than a diagnostic study. Thus, fifty sets of slides were read in one sitting; only one set was available for each patient; the test could not be run on more slides; and no consultations were allowed. On the other hand, it is possible that some of the observers simply made mistakes. Last, we think it unlikely that the disagreements resulted from a frequent source of poor reproducibility among observers in histopathologic diagnosis—a defect in classification (9).

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Propranolol-Induced Myotonia

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Abstract

Propranolol-induced myotonia has been described previously; however, the number of cases with associated muscle biopsy are few. An additional case is presented, and the possible relationship to subclinical myotonic dystrophy is discussed.

It is quite clear that propranolol exerts multiple effects on muscle metabolism (1–3). We have recently examined a patient who we believe represents a case of propranolol-induced myotonia, a condition previously described (4–5). Because of the increasingly widespread use of this drug, we report yet another example of this phenomenon.

Case Report. A 20-year-old woman initially consulted us for headaches occurring two to three times monthly. An aura of left hemidysesthesias was followed 15 minutes later by right unilateral throbbing headaches, lasting several hours to a day or more. No other neurologic symptoms were reported. Neurological and general physical examination were entirely within normal limits. No hormonal therapy was being used. The family history was unobtainable. A diagnosis of complicated migraine was made and propranolol 20 mg four times a day was begun. She was seen again months later, with more frequent headaches. The dose of propranolol was increased to 40 mg three times a day. The patient complained of stiffness in her hands. On examination, myotonia of the thenar eminence was clearly demonstrated. A history of the delivery of a healthy child eight months previously was elicited. There was some question of a subjective diminution of in utero movement. Some failure to thrive was described initially in the infant. It was not clear historically if the child had been floppy.

An electromyogram indicated myotonia. This diagnosis was confirmed at another institution.

Reexamination a month later revealed persistence of myotonia. Posterior subcapsular cataracts were not found. An EKG was normal. The propranolol was tapered, and within two months her myotonia disappeared. Migraine headaches recurred, prompting the readministration of propranolol in a dose of 40 mg three times a day, with resultant return of myotonia. Thyroid function including TSH was normal. Muscle biopsy of the left anterior tibialis showed mild type I atrophy.

Discussion. The mechanism of propranolol-induced myotonia is unclear. Blessing and Walsh (4) believed that their patient indeed had myotonic dystrophy which was only mildly expressed. We were unable to make a diagnosis of myotonic dystrophy on this patient despite the fact that several clinical clues raised our suspicions. It is well known that mild expressions of myotonic dystrophy may exist. We wonder if there is some common link in patients who demonstrate propranolol-induced myotonia. Of the three patients previously described, none had a normal biopsy. Whether an intrinsic abnormality of muscle is required to demonstrate propranolol-induced myotonia is an interesting supposition.

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Mount Sinai Medical Center of Greater Miami

Mount Sinai Medical Center of Greater Miami is a 55-acre complex in a residential area of Miami Beach. The center is affiliated with the University of Miami School of Medicine.

History and Introduction

Patient care, research, medical and paramedical education, and community outreach are all offered at Mount Sinai Medical Center of Greater Miami, a private not-for-profit 700-bed acute-care teaching hospital. In an era of specialization and spirited individualism, this 35-year-old $150 million business continues to provide a broad spectrum of health care.

People of every race and religion, mostly from Miami and Miami Beach, come to the medical and dental outpatient clinics. Mount Sinai provides more than $5 million in free care annually to the medically indigent—without government tax support. In the care it offers its locality, Mount Sinai may be considered a community hospital. The local population is skewed to the elderly; 72% of the hospital's patient days have been covered by Medicare. But Florida residents share rooms with patients referred from Latin America and Europe. Specialized services include the Sleep Disorders Center, the Cancer Center, and the Pain Center, as well as cardiology, pulmonary medicine, orthopaedics, gastroenterology, dermatology, and thoracic and cardiovascular surgery. Pacemaker implants are available. The Department of Obstetrics and Gynecology offers expertise in infertility, family-centered maternity care, and pediatric services which encompass the hospitalized child, clinics for infants and children, and nurseries for newborn and high-risk infants.

For every in-patient visit to the hospital, more than two visits are made for ambulatory care—to the outpatient department; the emergency department, designated as a trauma center; and ambulatory surgery, which offers more than 200 procedures, including hernia repair, laser surgery, and cataract surgery. Cataract repair entailing intraocular lens implants can be done in a single day.

Diagnosis is aided by the latest radiological technology, including the complex new nuclear magnetic resonance imaging, positron emission tomography, one of the world's largest medical cyclotrons, digital radiography, and comprehensive ultrasound services. The Department of Pathology and Laboratory Medicine is a referral center offering expertise in such specialized areas as bone marrow transplants.

The Biomedical Research Institute has some of the country's most sophisticated laboratory equipment and facilities. Investigations instituted at the center encompass treatments for Alzheimer's disease, the action of enzymes on the mechanical stability of the spine, the effectiveness of aspirin in preventing sunburn, and smoking and asthma studies.

The center carries on 143 residencies and fellowships and technical training in schools of nuclear medicine, ultrasound, and medical and radiologic technology.

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Iatrogenic Disease: An Overview

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Abstract

Iatrogenic disease is the result of a medical intervention or encounter, which could be in the form of drugs or procedures (medical or surgical) used for prophylaxis, diagnosis, or treatment. The incidence of iatrogenic disease in the last 20 years has not decreased but probably has increased as modern technological developments have produced more potent drugs and a large variety of invasive and noninvasive procedures. The incidence of drug reactions causing hospitalization varies from 3% to 7% and the incidence of drug reactions during hospitalization varies from 7% to 34%. Iatrogenic events due to diagnostic and therapeutic procedures in the hospitalized patient seem to have increased fourfold in the modern hospital compared to the 1960 hospital. Of the iatrogenic episodes related to procedures, 28% are classified as major. Diagnostic difficulties and the concept of pseudoiatrogenic disease are discussed. A series of risk factors for iatrogenic disease, as well as some of their probable mechanisms, are identified. Prevention of iatrogenic disease depends largely on physician education, awareness of risk factors, and the judicious use of risk-benefit analysis before any medical intervention. Considerable savings in money and human suffering would follow if the frequency of adverse events could be reduced.

Definitions. The word "iatrogenic" comes from the Greek word *iatreia*, "art of healing." The Webster's New Collegiate Dictionary (1) defines "iatrogenic" as "induced inadvertently by a physician or his treatment."

For the purpose of this review we will define iatrogenic disease as any illness that is caused by a medical intervention or encounter. Medical interventions can be in the form of drugs or the use of medical or surgical procedures. The indication for the iatrogenic medical encounter can be prophylaxis, diagnosis, or therapy. Finally, the iatrogenic mechanism can be an adverse outcome or an error of omission or commission.

Incidence and Etiology

The overall incidence of iatrogenic episodes in two studies performed almost 20 years apart is compared in Table 1. In 1964 Schimmel (2) reported that 20% of 1,014 patients admitted to a medical service suffered one or more episodes of iatrogenic illness; 4.7% were major episodes with a mortality of 1.6%. In 1981, Steel et al (3) reported 815 patients admitted to a general medical service (including medical intensive care unit, coronary care unit, metabolic unit and two general medical wards but excluding oncology patients' floor). Of these, 290 had one or more iatrogenic illness for a total of 497 iatrogenic illnesses; major complications defined as life-threatening, or as producing serious disability present at discharge, were found in 9% of the patients and were believed to have contributed to the death of 1.8% of all patients.

The incidence of adverse drug reactions causing hospitalization has been reported by several authors (Table 2). Seidl et al (4) and Smith et al (5) found that 3.9% of all admissions to a medical service were due to a drug-induced illness. Hurwitz (6) and Caranasos et al (7) found a 2.9% in-

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TABLE 1
Iatrogenic Episodes in Hospitalized Patients

Authors and Study Year	Total No. Pts.	Iatrogenic Episodes		Mortality	
		Pts. (%)	Episodes (% Major)	Pts.	(%)
Schimmel (2) 1960–61	1,014	198 (20)	240 (4.7)	16	(1.6)
Steel et al (3) 1979	815	290 (36)	497 (9.0)	15	(1.8)

TABLE 3
Incidence of Adverse Drug Reaction During Hospitalization

Authors and Study Year	Total No. Pts.	Pts. with Drug Reactions		Major Reactions
		No.	(%)	%
Schimmel (2) 1960–61	1,014	103	10.0	11.8
Seidl et al (4) 1964	714	97	13.6	6.8
Smith et al (5) 1965	900	97	10.8	—
Ogilvie et al (9) 1965–66	731	132	18.0	34.6

cidence of admissions due to adverse drug reactions. Trunet et al (8) sampled 325 consecutive admissions to the intensive care unit and found that 41 patients (12.6%) were admitted because of iatrogenic disease; 7.1% were due to a drug adverse effect or a drug therapeutic error, while 5.5% were due to a medical or surgical procedure. Of all cases with iatrogenic illness, 46.3% were the result of potentially avoidable errors; there were eight fatalities (2.5%) and 13 cases of life-threatening disease (4%).

The incidence of adverse drug reactions during hospitalization has been found in different series to be from 10% to 18% (2, 4, 5, 9), as shown in Table 3. The Boston Collaborative Drug Surveillance Program (10), monitoring 26,462 patients admitted to the medical wards of acute-disease hospitals in seven countries, found 24 drug-induced deaths for an overall death rate of 0.9 per 1,000 patients. Six were preventable deaths (five cases of pulmonary edema due to excessive intravenous fluids and one case of lethal arrhythmia due to hyperkalemia and administration of potassium chloride). Heparin was the drug responsible for a majority of drug deaths in reasonably healthy patients. Ogilvie and Ruedy (9) found that 60% of all adverse drug reactions were caused by four drugs or drug groups: digitalis and quinidine, antimicrobials, insulin, and diuretics.

TABLE 2
*Incidence of Adverse Drug Reaction Causing Hospitalization**

Authors and Study Year	Total No. Pts.	Pts. with drug reactions No. (%)
Seidl et al (4) 1964	714	28 (3.9)
Smith et al (5) 1965	900	35 (3.9)
Hurwitz (6) 1965–66	1,268	37 (2.9)
Caranasos et al (7) 1969–72	6,063	177 (2.9)
Trunet et al (8) 1978–79†	325	23 (7.1)

* Excluding suicide attempts and drug abuse.

† Admissions to multidisciplinary medical intensive care unit only.

Steel et al (3) found that drugs were the most common hospital intervention leading to iatrogenic illnesses (42% of all complications) in a general medical ward; diagnostic and therapeutic procedures accounted for 35% of all complications and a miscellaneous group including falls, transfusions, and diet accounted for 23%. But the percentage of serious complications caused by diagnostic and therapeutic procedures (28%) was greater than that in the other two categories ("drugs" and "miscellaneous").

Even when reports are not totally comparable (2, 3), they show that the modern hospital apparently has a greater incidence of iatrogenic episodes related to diagnostic and therapeutic procedures than the hospital of 20 years ago—an episode/patient ratio of 0.21 and 0.05 respectively (Table 4).

In the surgical field, Couch et al (11) screened 2,500 general surgical patients for "surgical misadventures," defined as misadventures resulting from a decision that was clearly an error in the field of general surgery; 56 important errors were found in 36 patients, an overall incidence rate of 1.4%. A total of 61 complications resulted from these general surgical misadventures. Of the entire group, 69% (25 of 36) had poor outcomes; there were 20 deaths for an overall mortality rate of 55% in the group with iatrogenic complications. Surgical errors were an important contributing factor in 11 of 20 deaths (55%). Of all errors, 62% were therapeutic errors of commission; the predominant example appears to have been in-

TABLE 4
Iatrogenic Episodes Related to Diagnostic and Therapeutic Procedures

Authors and Study Year	Total No. Pts.	Episodes No. (% Major)	Episode/Pt. Ratio
Schimmel (2) 1960–61	1,014	53 (28)	0.05
Steel et al (3) 1979	815	175 (28)	0.21

sufficient restraint and deliberation, excessive haste, impatience, overconfidence, and inadequate peer-group consultation. Seventy-eight per cent of the errors were made by board-certified surgeons.

One example of the identification of unexpected iatrogenic disease occurring years after a medical encounter is a report by Maxon et al (12) that significantly more thyroid gland tumors, both benign and malignant, were found in a group of 1,266 adults who had received external radiotherapy for benign diseases in childhood, when compared to a matched control group.

A totally new challenge is the area of iatrogenic disease related to long-term use of drugs to correct risk factors identified in relatively asymptomatic populations (13). Clofibrate used as a lipid lowering agent was found to be linked to an increased mortality rate from noncardiovascular causes including cancer. Many beta-blocking drugs raise serum triglycerides and lower high-density lipoprotein cholesterol, raising the question of their long-term risk-benefit ratio.

Types of Iatrogenic Disease. In hospitalized medical patients, aspiration pneumonia, nosocomial infections, and complications of invasive procedures accounted for most of the major complications in the series by Steel et al (3). Cardiopulmonary complications and infections made up 38% of all complications. The iatrogenic diseases that prompted admission to the intensive care unit in Trunet's series (8) were infections and inflammation (34%), acute renal failure (20%), neurological complications (17%), cardiopulmonary complications (15%), and bleeding (12%).

In the surgical series (11) intra-abdominal sepsis was the most common complication (25% of all complications) due to a surgical misadventure.

Diagnostic Difficulties and Pseudo-Iatrogenic Disease. The diagnosis of iatrogenic disease may at times be very difficult because the physician cannot be sure whether a particular event or complication is due to the natural history of the underlying disease or to a drug or procedure. Diseases or complications caused by the omission of an indicated medical or surgical intervention (iatrogenic disease due to errors of omission) are for the most part difficult to recognize.

A pseudo-iatrogenic disease can be defined as a spontaneous disease or complication that mimics disease caused by drugs or medical or surgical interventions. Examples of drug-related pseudo-iatrogenic disease would be a patient with systemic lupus erythematosus taking corticosteroids who develops acute psychosis or myopathy or aseptic necrosis of bone; sometimes it is very difficult to determine whether the complication was due to the underlying disease or to the use of corticosteroids. An interesting example of procedure-related pseudo-iatrogenic disease is reported by Hildner et al (14). They compare complications that occurred immediately before or after 1,606 diagnostic cardiac catheterizations: procedure-related complications, defined as incidents that occur during or after catheterization, were seen in 0.81% of the cases with no mortality; pseudocomplications (pseudo-iatrogenic diseases), defined as spontaneous incidents that occur during the 24-hour period before the scheduled catheterization, were also seen in 0.81%, with 4 (0.24%) deaths. Complications were strikingly similar in both groups except for three instances of vascular injury; the authors conclude that it is likely that similar disease-caused incidents occur after catheterization and are not necessarily procedure-related: a good illustration of the difficulties and pitfalls in the diagnosis of iatrogenic disease.

Risk Factors. The most important recognized risk factors for iatrogenic disease are as follows.

Hospitalization is nowadays as much a risk factor as it was 20 years ago (Table 2). The growing number of invasive diagnostic and therapeutic procedures and the ever-expanding number of potent drugs are recognized etiologic factors in iatrogenic disease in the modern hospital. Today more than ever the physician has to make difficult judgments in evaluating the risk-benefit ratio of medical interventions.

The need for simultaneous application of many of these interventions in seriously or critically ill patients makes these patients especially high risks for iatrogenic complications, compounding the risks of each drug or procedure with the risks of drug interactions and drug-procedure interactions. Steel et al (3) found that house officer's assessment of "critical to poor" condition on admission was associated with a higher iatrogenic complication rate than was the assessment of "stable to good."

Length of hospitalization is a major feature that distinguished patients with adverse reactions from other patients (2, 4, 6, 9), as shown in Table 5. It is not clear whether this is a result of or a causative factor in the added complication.

Admission from another hospital or from a nursing home was associated with higher incidence of iatrogenic complications than was admission from home or housing facility (3). Patient's age, sex, and admission location (into intensive care unit, coronary care unit, or ward) did

TABLE 5

Iatrogenic Disease and Length of Hospitalization (Days)

Authors	All Pts.	Pts. with drug reactions	Other Pts.
Schimmel (2)	12.0	28.7	11.4
Seidl et al (4)	14.3	20.8	—
Ogilvie & Ruedy (9)	13.7	20.5	11.6
Hurwitz (6)	15.0	21.0	—

not affect the chance of iatrogenic complication in this study.

The geriatric patient is thought to be at increased risk of iatrogenic complications due to a number of factors. Elderly individuals very commonly have more than one chronic disorder requiring the use of multiple drugs, increasing the probabilities of adverse drug interactions. The peculiarities of drug disposition in old age have been recently reviewed (15, 16). Reduction in drug clearance due to decreased glomerular filtration in old age (mean 35% reduction) is a very important mechanism in drugs such as digoxin, quinidine, and theophylline that have narrow ranges of therapeutic serum concentrations above which toxicity is likely to occur. Changes in body composition with age may influence drug distribution; lean body mass declines and adipose tissue mass increases. Some drugs (acetaminophen, antipyrine, ethanol) are relatively water-soluble and lipid insoluble and their distribution to tissues in the elderly may decrease. Lipid-soluble drugs (diazepam, lidocaine) may become more extensively distributed in the elderly. On the other hand, serum albumin tends to decrease with age, so that for highly protein-bound drugs, a higher percentage of the drug will be unbound and pharmacologically active in the elderly.

A history of prior drug reaction or of allergic disease also puts a patient at risk.

The physiologic mechanisms and pharmacologic effects of drug interactions are summarized in Table 6. The clinician must be aware of an ever-increasing body of scientific knowledge related to drug toxicity and drug interactions. In the future, computer-assisted data retrieval will be within physicians' day-to-day reach to help them cope with this problem.

Cost

Couch et al (11) figured an average of $40,000 in excess expense and an average of 40 days of excess hospitalization for the 36 patients who sustained surgical errors among 5,612 surgical admissions.

TABLE 6

Drug Interactions

Physiologic mechanism	Pharmacologic effect
Absorption: interference	decreased drug plasma concentration
Distribution: displacement from binding sites	higher level of pharmacologically active drug
Biotransformation:	
enzyme induction	decreased drug activity
enzyme inhibition	increased drug activity
Excretion: decreased renal clearance	increased drug plasma concentration
Additive effect	enhanced pharmacologic effect

Zook and Moore (17) found that approximately 12% of the most costly 20% of patients were admitted because of an unexpected complication during treatment, including side effects of treatment, misdiagnosis, and drug reactions. This study found that 13% of hospitalized patients use as much of the resources as the remaining 87% of patients in a given year. It can be concluded that patients who have complex illnesses also suffer from a large number of adverse developments. The cost of iatrogenic disease is not known, but considerable savings in money and human suffering would follow if the frequency of adverse events could be reduced.

Prevention

Prevention of iatrogenic illnesses is a difficult task because of the multiple factors that may interplay in their etiology (18). In-hospital monitoring of patients with adverse outcomes may be a most economically efficient method (11); education of physicians to make them aware of the risk factors should be emphasized; patients with multiple chronic conditions requiring multiple drugs or multiple diagnostic and therapeutic procedures are at great risk. Knowledge of multiple drug interactions is essential in these times of potent pharmacologic agents. Awareness of the peculiarities of the geriatric population and their great susceptibility to hospitalization-related complications is essential in this era of increasing numbers of elderly patients.

In times of ever-expanding technology, the physician has to be, more than ever, aware of the Latin dictum *Primum non nocere*. The risk-to-benefit ratio of every medical intervention should be carefully evaluated before introducing drugs or performing diagnostic or therapeutic procedures. As Mack Lipkin has lucidly stated (19):

"While we become steadily more successful in prolonging life, we also become more capable of prolonging suffering. At the same time that our drugs become ever more effective in giving help, they become more potent in doing harm."

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Effect of Inhaled Ipratropium Bromide on Tracheal Mucociliary Transport in Bronchial Asthma

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Abstract

Bronchial asthma is characterized by increased airway smooth-muscle tone and excessive airway secretions due to hypersecretion and diminished clearance of mucus. For this reason, atropine, which is a potent bronchodilator but interferes with mucociliary clearance, has not gained wide acceptance in the treatment of bronchial asthma. In the present study of 14 patients with bronchial asthma, we assessed the effects of ipratropium bromide, a new atropine analog, on respiratory and mucociliary function. Tracheal mucous velocity and the forced expiratory volume in one second (FEV_1) were measured before and serially for 120 minutes following the inhalation of either 40 μg ipratropium bromide or placebo in a double-blind cross-over design. Baseline mean tracheal mucous velocity and FEV_1 were comparable before the two treatments. Neither ipratropium bromide nor placebo had a significant effect on mean tracheal mucous velocity throughout the 120-minute observation period. Mean FEV_1 was slightly higher following ipratropium bromide than following placebo ($p < 0.05$). These results suggest that, at the dosage used, inhaled ipratropium bromide reduced airflow obstruction without an appreciable effect on mucociliary transport in the central airways, where the drug concentration is the highest.

The anticholinergic agent ipratropium bromide is an effective bronchodilator in patients with chronic bronchitis and bronchial asthma (1, 2). Since other anticholinergic agents, such as atropine and hyoscine, impair airway mucociliary function (3–6), similar adverse effects were originally expected for ipratropium bromide. It was subsequently shown that the airway clearance of inhaled radioactive aerosols is not altered by ipratropium bromide in normal subjects or in patients with bronchial asthma and chronic bronchitis (1, 2, 7). However, in those studies overall mucociliary clearance was measured without selecting out central airways, where one would expect the highest mass deposition and hence tissue concentration of the inhaled drug. We therefore evaluated the effect of inhaled ipratropium bromide on respiratory function and tracheal mucociliary transport in subjects with bronchial asthma.

Methods. Fourteen subjects with the clinical diagnosis of allergic bronchial asthma were studied, each giving informed consent for participation. All subjects gave a history of episodic wheezing and had cutaneous and bronchial reactions to ragweed antigen. They were asymptomatic at the time of the study, had not had a recent viral respiratory infection, and had not smoked cigarettes for at least one year. Concomitant medications included antihistamines (2 subjects), inhaled beta-adrenergic agonists (8 subjects), methyl xanthines (6 subjects), cromolyn sodium (1 subject), and oral glucocorticosteroids (1 subject). All medications were withheld for at

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least 12 hours prior to testing. Each subject was studied between 0900 and 1200 hours on two days, separated by a washout period of 2–7 days. After determinations of baseline forced expiratory volume in one second (FEV_1), baseline tracheal mucous velocity was measured as described by Friedman et al (8). The subject was seated in a dental chair. After topical anesthesia of his upper airway with 2% lidocaine solution, bismuth-impregnated Teflon discs (1 mm in diameter) were insufflated through the larynx into the trachea using a transorally introduced fiberoptic bronchoscope (Olympus BF-5B2) whose tip was positioned in the pharynx. The fiberoptic bronchoscope was then removed, and the cephalad motion of the Teflon discs recorded for one minute on videotape (using a fluoroscopic unit provided with image intensifier and a TV camera). From this, the velocity of 6–10 Teflon discs was measured to obtain a mean tracheal mucous velocity. The whole procedure (excluding the data analysis) lasted less than seven minutes.

After these baseline measurements, the subjects inhaled from a metered dose canister either two whiffs of 20 μg ipratropium bromide (total dose 40 μg) and freon propellant or two whiffs of placebo (freon propellant alone). This was done on two experimental days, using a double-blind cross-over design. Seven patients were randomly assigned to each sequence group (ipratropium bromide followed by placebo, or placebo followed by ipratropium bromide). The canister was held between the lips and activated immediately after the beginning of a slow inspiratory capacity maneuver (two whiffs per maneuver). After drug or placebo inhalation, the measurements of pulmonary function were repeated at 30, 60, and 120 minutes. To compare the effects of ipratropium bromide with those of placebo on tracheal mucous velocity and FEV_1, the parameters were analyzed at each time, using baseline as a covariate. The model included subject, treatment, and visit effects. Adjusted means from the analysis of variance are presented for each time.

Results. Mean baseline tracheal mucous velocity and FEV_1 were comparable and not significantly different on the two experiment days (see Table). Mean tracheal mucous velocity was slightly higher following the inhalation of placebo than following inhalation of ipratropium bromide, at both 30 and 120 minutes after administration. However, these differences were not significant. Mean FEV_1 was higher following ipratropium bromide than following placebo at all times of measurement ($p < 0.05$).

TABLE

Effects of Ipratropium Bromide on Tracheal Mucous Velocity and FEV_1

(14 Subjects)

		After Inhalation*		
	Baseline*	30-Min.	60-Min.	120-Min.
Tracheal mucous velocity (mm min)				
Ipratropium bromide	4.9(1.1)	4.8(1.0)	—	5.0(0.9)
Placebo	4.4(0.9)	6.3(1.2)	—	6.0(1.0)
FEV_1				
Ipratropium bromide	2.99(0.25)	2.94(0.24)†	2.92(0.24)†	3.10(0.25)†
Placebo	2.93(0.23)	2.72(0.24)	2.60(0.28)	2.77(0.23)

* Mean (S.E.).

† Different from placebo ($p < 0.05$).

Discussion. The presence of excessive airway secretions that are difficult to expectorate is a typical clinical feature of patients with bronchial asthma. That increased airway secretions play an important role in bronchial asthma has also been suggested by pathologic studies which have demonstrated generalized mucous plugging of the bronchial tree in patients who died in status asthmaticus, and mucous plugging of peripheral airways in patients with stable asthma (15). This accumulation of lower airway mucus seems to result from both mucus hypersecretion and impaired mucociliary clearance (11, 16, 17). The latter impairment has been shown to be present in symptomatic and asymptomatic patients with bronchial asthma (15). In the present study, involving asthmatic patients in remission, mean baseline tracheal mucous velocity was 4.4 and 4.9 mm/min on the two experiment days. These values are comparable to the mean of 6.3 mm/min (55% of age-matched controls) reported by Mezey et al (11) in another group of asymptomatic asthmatics.

Since bronchial asthma is associated with mucociliary dysfunction, bronchodilators which inhibit the clearance of airway secretions are generally used with caution. Fortunately, beta-adrenergic agonists and methyl-xanthines are not only potent bronchodilators but also stimulate mucociliary clearance (18). However, this is not true of the classical anticholinergic agents, which appear to have opposing effects on respiratory and mucociliary function.

Several studies have demonstrated the bronchodilator effects of atropine (9, 10) and its analog ipratropium bromide (1, 2). This was confirmed by the present study which showed a slightly but significantly higher FEV_1 after inhalation of 40 μg ipratropium bromide than after placebo inhalation. This difference was primarily due to a decrease in FEV_1 after placebo. It cannot be determined from this study if this decline was caused by the placebo (freon) or reflected a diurnal variation. In either case, ipratropium bromide prevented the decrease in FEV_1. Mean baseline FEV_1 measurements were 86% and 85% of predicted normal on the ipratropium and placebo days, respectively. If a higher degree of airflow obstruction had been present, a more substantial bronchodilator effect of ipratropium bromide might have been observed.

While the detrimental effects of inhaled or systemic atropine on mucociliary function in the airways have been generally well established (3, 5, 6, 12), ipratropium bromide at therapeutic dosages has been shown not to depress overall mucociliary clearance in controls or in patients with airway disease (1, 2, 7). We reasoned that during inhalation of ipratropium bromide, the highest drug concentration would be present in the central airways including the trachea (13). A depression of mucociliary function by ipratropium bromide could therefore occur in the trachea only and not be reflected by changes in overall mucociliary clearance of the lung. However, our results show no decrease in tracheal mucous velocity after 40 μg ipratropium bromide in patients with bronchial asthma. Freon placebo produced a slight (insignificant) stimulation of tracheal mucous velocity, an effect which we have previously observed (14). Our results are also in keeping with those of Sackner et al (12), who failed to demonstrate a depression of tracheal mucous velocity by ipratropium bromide in anesthetized dogs.

We conclude that in asymptomatic asthmatic subjects, inhaled ipratropium bromide at a dosage of 40 μg has no appreciable effect on mucociliary transport in the central airway where the drug concentration can be expected to be the highest. This indicates that with respect to airway secretions ipratropium bromide may be a safe bronchodilator.

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Papillomas of Prostatic Urethra with Prostatic-Type Epithelium: Report of Eight Cases

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Abstract

Eight cases of so-called adenoma with prostatic-type epithelium are described. Since the lesions are mainly papillomatous, we feel a more apt name is papilloma with prostatic-type epithelium. The lesion is probably not as rare as has been thought, and it is definitely not exclusively a disease of young men. The prostatic nature of the epithelium has been demonstrated by immunoperoxidase staining of the lesions for prostate-specific antigen and prostatic acid phosphatase.

Benign polypoid and papillary tumors of the prostatic urethra are uncommon. They have been divided into three distinct types (1). One type is the inflammatory pseudopolyp which is seen in the urethra of men and women. Another type, occuring primarily in young boys, is the pedunculated polyp with a fibrous stroma and surface transitional epithelium with centrally located mucous glands. These polyps usually occur on or adjacent to the verumontanum and cause urinary obstruction. A third type, occurring in the prostatic urethra and described as rare in the AFIP Fascicle, is a papillomatous lesion known as adenomatous polyp with prostatic-type epithelium (2). Other names have been used for this lesion since it was described by Randall (3) under the name of benign glandular polyp. These include benign polyps with prostatic-type epithelium (4); adenomatous polyps of the prostatic urethra (5); benign polyps in the prostatic urethra (6); prostatic urethral polyps in adults (7); and ectopic prostatic tissue in the urethra (3).

These prostatic urethral polyps have been considered lesions of young men. Butterick (8) reported on 68 cases involving the urethra, with a mean age of 31 years and a peak incidence of between 15 and 20 years. All of his cases but two were in the prostatic urethra, and all were either on the verumontanum or immediately adjacent to it.

We report eight cases of urethral polyps with prostatic-type epithelium in which the prostatic nature of the epithelium is confirmed by application of immunoperoxidase methods for identification of prostatic specific antigen and prostatic acid phosphatase (see Table).

Methods. Appropriate slides were stained with hematoxylin and eosin (H & E), periodic acid Schiff (PAS), and PAS after diastase digestion. All cases were studied by the peroxidase-antiperoxidase method for prostatic-specific antigen and prostatic acid phosphatase using commercial kits (Dako-Pap Kit-Prostatic Specific Antigen; Immulok-Histoset-Prostatic Acid Phosphatase).

Pathology. The tumors consisted of numerous papillae composed of a core of well-vascularized fibrous tissue without muscle fibers, surfaced with tall columnar cells with basal nuclei. Below

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TABLE
Papilloma with Prostatic-type Epithelium
(Eight Cases)

Pt. No.	Age	Presenting Symptoms	Location of Lesion	Additional Findings
1.	49	Persistent microscopic hematuria	Prostatic urethra	
2.	84	Painless hematuria, urinary obstruction	Prostatic urethra	Hyperplasia of bladder neck
3.	71	Gross painless hematuria, mild urinary obstruction	Prostatic urethra	Well-differentiated papillary transitional cell carcinoma of lateral bladder wall
4.	62	Urinary obstruction	Prostatic urethra	Prostatic hyperplasia
5.	72	Urinary obstruction, high clinical suspicion of prostatic carcinoma	Prostatic urethra	Prostatic hyperplasia
6.	55	Painful erections, microscopic hematuria	Prostatic urethra	Prostatic hyperplasia
7.	46	No G.U. symptoms, history of seminoma 19 years earlier, huge retroperitoneal malignant fibrous histiocytoma	Trigone of bladder	Retroperitoneal malignant fibrous histiocytoma
8.	66	Urinary obstruction, high clinical suspicion of prostatic carcinoma	Prostatic urethra	Prostatic hyperplasia and prostatic adenocarcinoma

the epithelial cells were distinct myoepthelial cells. The cytology of the epithelium lining the papillae was identical to that seen in periurethral prostatic glands (Fig. 1, 2). PAS stains showed granular PAS positivity in the cytoplasm of epithelial cells with occasional larger PAS-positive droplets. On PAS stain after diastase digestion, the fine granularity disappeared but the droplets persisted. The PAS stain also defined a delicate, focally interrupted basement membrane. Immunoperoxidase staining for prostate-specific antigen and prostatic acid phosphatase showed positivity in the cytoplasm of the columnar epithelial cells, but not of the myoepithelium or any of the cells making up the stroma (Fig. 3).

Discussion. Eight cases are described in which papillary polyps of the prostatic urethra with prostatic epithelium resulted in hematuria or symptoms of obstruction. The average age in these eight cases is 63 years (range 46 to 84 years), higher than and in striking contrast to the much younger age in previous reports (6, 8). Part of the variation may reflect the elderly population served by the hospitals from which the report emanates, but we feel it is mainly due to our high awareness of the lesion since we first identified it in a 49-year-old man whose cause of hematuria was strictly related to a papilloma with prostatic-type epithelium removed from the prostatic urethra. Most of our cases come from men with en-

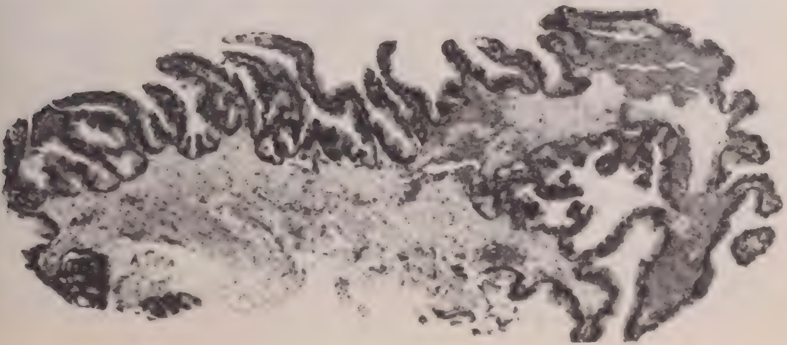

FIG. 1. Low-power view of specimen showing papillary nature of the tumor. What appear to be shallow glands at the bases of some papillae are seen.

larged prostates whose symptoms were assumed to be the result of prostatic hyperplasia.

We also feel that papilloma with prostate-type epithelium of the prostatic urethra occurs more frequently than indicated in previous publications (2). The eight cases discussed here were all discovered over a period of 11 months.

In Butterick's series, hematuria was the main complaint in two-thirds of the cases, almost half complaining of dysuria and urinary frequency. Hematuria was seen in five of our cases. Butterick's lesions were morphologically similar to ours, although a few of his cases had a few bands of smooth muscle in the stroma, and all had small irregular basophilic bodies in the cytoplasm of epithelial cells on H & E stain that were positive on PAS staining.

Neither our cases nor those described in the literature had a significant inflammatory reaction. so there is little likelihood that inflammation is a pathogenic factor. Randall (3) considered the lesion as "probably prostatic in its origin and representing early benign hypertrophy, possibly in a tuft of aberrant prostate tissue." Nesbit (6) and Butterick (8) demonstrated acid phosphatase in the cytoplasm of some of their cases, suggesting that the epithelium was indeed prostatic. Butterick (8) showed similarities on electron microscopy between polyp epithelium and hyperplastic prostate epithelium. Walker (9) demonstrated that the cells were positive using immunoperoxidase stains with prostate specific antigen and prostatic acid phosphatase.

Embryologically, the prostate gland develops as outgrowths of the endodermal urethral epithelium, above and below the entrance of the male ducts. It is therefore not surprising that rests of prostate tissue could conceivably proliferate in adult life. Indeed it is questionable whether the so-called adenomatous polyps with prostatic-type epithelium are tumors or whether they merely represent hyperplasia in ectopic prostatic tissue, as suggested by Randall (3). Lesions similar to the adenomatous polyp with prostatic-type epithelium have been described in the urinary bladder (10, 11). Their origin has been ascribed to unexplained alterations in the glands of Albarran which develop by evagination of endodermal epithelium of the embryo at the neck of the bladder. The epithelium from which the glands of Albarran and the prostate develop is similar, and that ectopic lesions with similar ep-

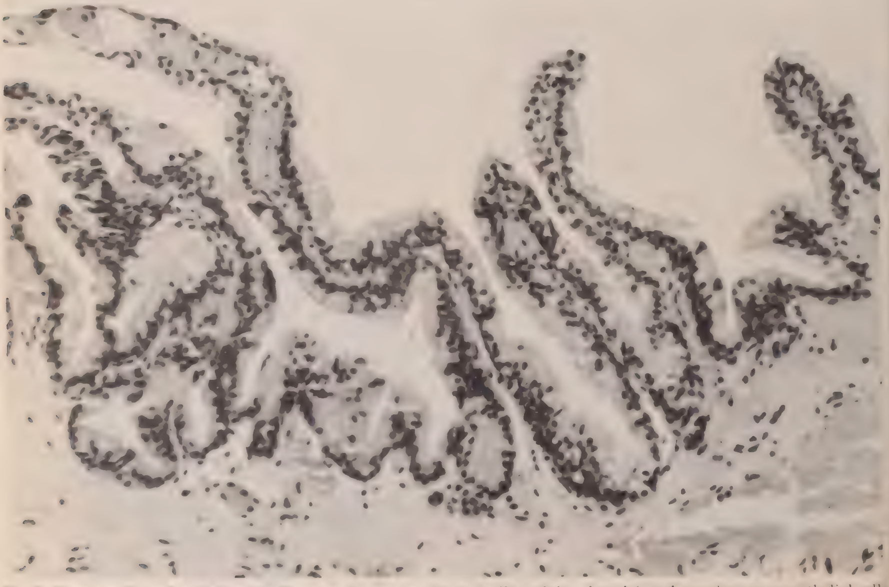

FIG. 2. Some papillary fronds showing fibrovascular core, epithelial cells with basal nuclei, and prominent myoepithelial cells.

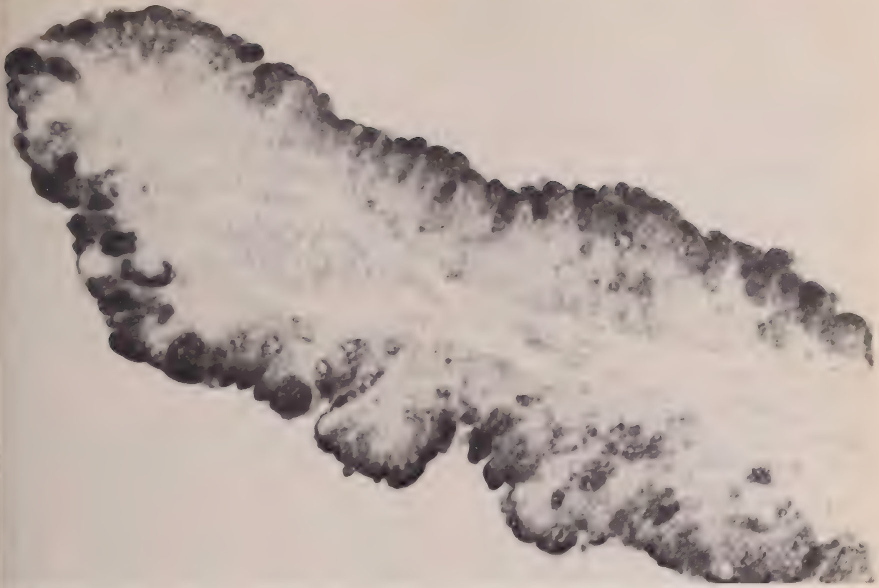

FIG. 3. High-power view of a single papilla stained with prostate-specific antigen by immunoperoxidase method.

ithelium occur in the prostatic urethra and the bladder is not surprising. Our case no. 7 is such an example.

Whether the adenomatous polyp with prostatic-type epithelium represents early benign prostatic hyperplasia is a questionable point. We feel it does in most of our cases.

We have described cases of so-called adenomatous polyp with prostatic-type epithelium of the prostatic urethra. Since the lesions are mainly papillomatous, perhaps a more apt name might be papilloma with prostatic-type epithelium. We have demonstrated by means of immunoperoxidase staining methods that the lesion is indeed composed of prostatic-type epithelium.

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Effects of Hydrocodone Bitartrate on Breathing Pattern of Patients with Chronic Obstructive Pulmonary Disease and Restrictive Lung Disease

MARVIN A. SACKNER, M.D.

Abstract

Patients with chronic obstructive pulmonary disease and restrictive lung disease usually have an elevated respiratory-center drive. This is manifested by an abnormal pattern of breathing, namely, an increased mean inspiratory flow ($V_T T_I$) and minute ventilation (V_{min}), and an inspiratory time (T_I) usually less than one second in duration. Their perception of breathlessness may relate to this pattern of breathing. Hydrocodone bitartrate as Hycodan, a mild narcotic, was administered to such patients and their respiration was monitored noninvasively to ascertain whether depression of respiratory drive by this agent to produce a breathing pattern closer to normal would not excessively depress ventilation. This procedure was carried out as an initial step to a trial of long-term treatment for dyspnea. Hydrocodone bitartrate decreased $V_T T_I$ and V_{min} and lengthened T_I, and therefore improved the breathing pattern. In no instance did ventilation decrease below the normal range. Therefore, hydrocodone bitartrate, with close surveillance, might have a place in long-term treatment of dyspnea in patients with chronic obstructive pulmonary disease and restrictive lung disease.

Although opiates had been used to relieve dyspnea associated with asthma and emphysema since the late nineteenth century, it was not until 30 years ago that their precipitation or aggravation of respiratory acidosis in such patients was recognized (1–3). The initial hazard was reported for morphine, but clinicians extrapolated this potential adverse effect to all narcotics, despite observations that different opiate derivatives at equivalent analgesic doses produced variable depression of ventilation (4). Further, a clinical survey suggested that patients with respiratory disease of equal severity varied greatly in their tendency to develop respiratory acidosis following administration of narcotics (5). Since current treatment of chronic obstructive pulmonary disease is at best only moderately effective (6), there is need for specific therapy of breathlessness. Portable oxygen provides symptomatic relief for some patients with chronic obstructive pulmonary disease (COPD), but is an inconvenient means of therapy. With this background, Woodcock and associates (7) assessed the effect of dihydrocodeine on breathlessness and exercise tolerance. This orally bioavailable opiate with a low potential for addiction reduced the subjective perception of breathlessness and increased exercise tolerance through reduction in ventilation and oxygen consumption.

Patients with COPD as well as those with restrictive lung disease display heightened respiratory-center drive, as reflected by an elevated

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TABLE 1
Characteristics of Patients

	Restrictive lung disease*	COPD*
Sex	5 M 3 F	8 M 9 F
Age-years	65 ± 10	66 ± 6
Vital capacity LBTPS	1.56 (.44)	1.85 (.56)
% Predicted	49 (18)	60 (15)
Residual volume LBTPS	1.85 (.44)	5.37 (1.60)
% Predicted	103 (23)	294 (77)
Total lung capacity LBTPS	3.44 (.72)	7.27 (1.68)
% Predicted	66 (12)	138 (23)
$FEV_{1.0}$ LBTPS	1.21 (.41)	.63 (19)
% Predicted	49 (15)	27 (8)
Airway resistance $cmH_2O/L/sec$	2.7 (1.0)	4.5 (1.3)
% Predicted	168 (80)	666 (180)
pH	7.48 ± .02	7.43 ± .04
PaO_2 mmHg	56 ± 11	66 ± 7
$PaCO_2$ mmHg	38 ± 8	41 ± 4

* Means (SD).

mean inspiratory flow when monitored noninvasively with respiratory inductive plethysmography (8). If this inappropriately increased respiratory drive contributes to dyspnea, then a mild narcotic which suppresses drive might provide symptomatic relief. Further, the pattern of breathing might be altered to lessen the work of breathing. Since marked depression of respiratory-center drive is deleterious and leads to respiratory acidosis, the purpose of the present study was to document acute effects as a step toward a long-term clinical trial. We selected hydrocodone bitartrate, an opiate derivative with a low potential for tolerance when used clinically as a cough suppressant.

Materials and Methods

Patients. Seventeen patients with chronic obstructive pulmonary disease and eight with restrictive lung disease were enrolled in the study. All complained of dyspnea on mild exertion and most had dyspnea at rest. The COPD patients were on aerosolized beta adrenergic agents, long-acting theophyllin preparations, and corticosteroids; five of the eight restrictive lung disease patients were taking corticosteroids at the time of the investigation. Their characteristics are listed in Table 1.

Theoretical Background. The traditional equation of minute ventilation ($\dot{V}_{min}$) indicates equality to the product of tidal volume (V_T) and respiratory frequency (f) such that $\dot{V}_{min} = V_T \times f$. This can be rewritten so that $\dot{V}_{min} = V_T/T_I \times T_I/T_{TOT}$. The first component, V_T/T_I, has been termed mean inspiratory flow, and the second, T_I/T_{TOT}, the fractional inspiratory time, or effective timing ratio. V_T/T_I reflects respiratory center drive and T_I/T_{TOT} is a crude indicator of airways obstruction (8, 9).

With respiratory inductive plethysmography, three signals are recorded: the calibrated rib-cage (RC) and abdominal (ABD) excursions and their electrical sum signal, the last being equivalent to tidal volume (V_T). The sum of the absolute values of the trough-to-peak excursions of RC and ABD, irrespective of their timing, to the tidal-volume signal is termed the "maximum compartmental amplitude (MCA)." When the peak-to-trough amplitudes of the RC and ABD signals are in phase, the ratio of MCA to V_T (MCA/V_T) is equivalent to 1.00. When the trough-to-peak amplitudes of the RC and ABD move out of phase with each other, MCA/V_T exceeds 1.00. Thus, this index provides information on overall phasic relations between RC and ABD excursions (8, 9).

Apparatus. Detailed descriptions of the respiratory inductive plethysmograph (Respitrace Corp., Ardsley, NY) have been published (10, 11). Briefly, the device consists of two coils of Teflon-insulated wire sewn onto elastic bands encircling the rib cage and the abdomen and connected to an oscillator module. Changes in the cross-sectional area of the RC and ABD compartments alter the self-inductance of the coils and the frequency of their oscillations, which, after appropriate calibration, reflect tidal volume measured by spirometry. Assuming that the respiratory system moves with two degrees of freedom, that is, the rib cage and abdominal compartments can be considered as the only two moving components, the device is calibrated using RC, ABD, and spirometric (SP) volumes and the equation $RC/SP + ABD/SP = 1$ (10). The subject breathes into a spirometer in two body postures to produce a spread of values of rib-cage and abdominal contributions to tidal volume, and the equation is solved graphically to achieve the scaling factors for the electrical gains of the RC and ABD amplifiers.

The signals from the respiratory inductive plethysmograph were recorded on a polygraph recorder (Grass Instruments, Quincy, Mass) and a Z-80A–based microprocessor system (Respicomp, Respitrace Corp., Ardsley, NY), which sampled the signals at 20 points/sec. It continuously calculated respiratory frequency, tidal volume, minute ventilation, inspiratory time, fractional

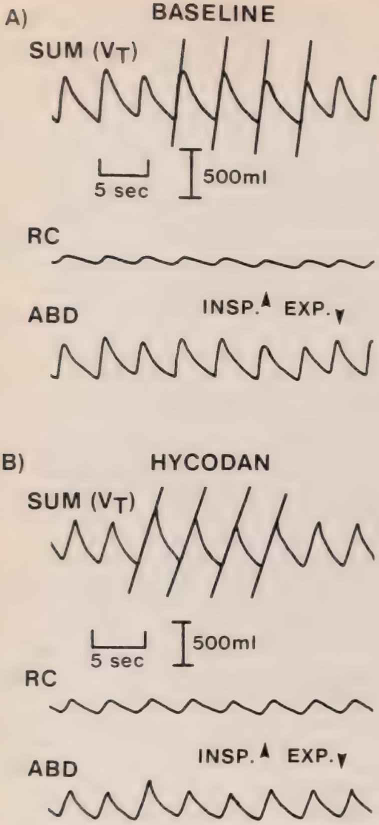

FIG. 1. Analog recording from respiratory inductive plethysmography: SUM (V_T) represents addition of rib cage (RC) and abdominal (ABD) compartmental excursions. Lines drawn on the tidal breaths of baseline (A) and Hycodan (B) tracings indicate slope of V_T/T_I. After Hycodan, this slope significantly decreases, a finding consistent with decreased respiratory center drive.

inspiratory time, mean inspiratory flow, the percentage of rib-cage contribution to tidal volume, and the ratio of the maximum compartmental amplitudes to tidal volume.

Procedure. The respiratory inductive plethysmograph (RIP) was calibrated and then validated against spirometry (SP) such that tidal volume from RIP fell within ±10% of SP. The patients then lay semirecumbent in a quiet room watching television for a minimum of 10 minutes prior to recording the breathing pattern for 15 minutes. Following the baseline recording, one tablet of Hycodan was administered; this contains hydrocodone bitartrate 5 mg and homatropine methylbromide 1 mg. About 50 minutes later, another 15-minute period of breathing pattern was recorded.

Results

A representative analog recording of breathing pattern was obtained with respiratory inductive plethysmography at baseline and after administration of one tablet of Hycodan (Fig. 1). The decrease of mean inspiratory flow after the administration of Hycodan is indicated by the more gradual slope of the inspiratory limb of the tidal-volume tracing compared to baseline.

Table 2 lists the means (and SD) of the breathing pattern components. Baseline values of frequency, tidal volume, minute ventilation, and mean inspiratory flow were elevated, whereas inspiratory time and fractional inspiratory time were reduced, compared to previously reported normal values (9). No differences in response to Hycodan were found between the COPD and restrictive lung disease patients so that the results were analyzed together. Hycodan produced a fall of V_T, $\dot{V}_{min}$ and V_T/T_I. T_I and T_I/T_{TOT} rose. There was no effect on f, $\%RC/V_T$, or MCA/V_T.

Wide variability in individual changes for $\dot{V}_{min}$ and V_T/T_I in response to Hycodan was recorded (Fig. 2), but no value fell below the normal range (11).

Discussion

The present study indicates that acute administration of Hycodan to patients at rest usually depresses respiratory center drive in patients with COPD or restrictive lung disease, as reflected by a decrease of mean inspiratory flow and minute ventilation. These results differ from those of Woodcock et al (7), who administered dihydrocodeine to COPD patients and found no change in resting minute ventilation, although

TABLE 2

Breathing Pattern Components 50 Minutes after Administration of Hycodan Tablet

	Baseline Mean (SD)	Post Hycodan Mean (SD)	p	% change
f (br/min)	23.8(6.2)	22.8(5.5)	NS	
V_T (ml LBTPS)	428(120)	406(129)	<.05	−5
$\dot{V}_{min}$ (LBTPS)	9.39(2.63)	8.62(2.48)	<.001	−8
T_I (sec)	.94(.15)	1.02(.17)	<.001	+8
T_I/T_{TOT}	0.352(.054)	0.368(.053)	<.02	+4
V_T/T_I (ml/sec)	462(107)	408(115)	<.001	−12
$\%RC/V_T$	55(20)	54(19)	NS	
MCA/V_T	1.06(.06)	1.05(.06)	NS	

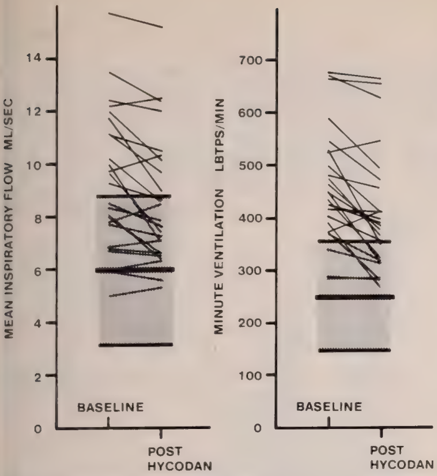

FIG. 2. Individual changes of mean inspiratory flow and minute ventilation following administration of Hycodan. Solid line and shaded area indicate mean ± 2 SD of normal values (11). These plots indicate the marked variability in response of pulmonary patients to Hycodan, but no value fell below the normal range.

submaximal exercise ventilation was reduced. The lack of change in ventilation reported by Woodcock et al (7) might be due to either the different narcotics administered or a masking of respiratory response because their patients breathed on a mouthpiece through a pneumotachograph (12). For example, when normal subjects have bronchospasm provoked by aerosolized methacholine, their mean inspiratory flow (V_T/T_I) does not change if they breathe on a mouthpiece through a pneumotachograph, but V_T/T_I does rise when breathing is unencumbered by an external connection to the airway (13).

The pattern of ventilatory response to Hycodan is similar to that observed in normal subjects given intramuscular morphine sulfate 0.2 mg/Kg. Morphine produces a 12% fall of ventilation due to reduced tidal volume without altering frequency (14). Hycodan reduced minute ventilation 8% primarily as a result of reduction of tidal volume.

Woodcock et al (7) found that during submaximal exercise, acute administration of dihydrocodeine produced a fall of oxygen consumption concomitant with a fall of ventilation. This might have been achieved by improvement in metabolic efficiency, with reduced heat loss, or possibly by a reduction in energy wasted because of excess postural tone or an abnormal pattern of breathing. With regard to the latter explanation, the significant reduction of V_T/T_I with Hycodan would produce a decrease in the resistive work of breathing which in the COPD patients might contribute to the perception of less breathlessness. No such effect would be expected in restrictive lung disease patients in whom airway resistance was normal.

Woodcock et al (7) were encouraged by their study but were concerned about the risks of respiratory depression and addiction to opiate drugs over the long term. We administered Hycodan to our patients in the dose of one tablet three times a day if $\dot{V}_{min}$ did not decrease or fell only up to 20% of baseline with the acute administration of Hycodan. If there were a greater decrease of $\dot{V}_{min}$, then the initial Hycodan dose was 1/2 tablet three times a day. Eight of the 25 patients took Hycodan less than one month and stopped it because dyspnea was not relieved. Subjective relief of dyspnea was accomplished in 12 of 17 COPD patients and 5 of 8 restrictive lung disease patients. This improvement was manifested by statements such as "I now can get through the washing and dressing early in the morning because I'm more relaxed" and "I can walk further without getting as breathless." Subjective side-effects included mild constipation and drowsiness. The dosage for most patients whom we have followed for up to 2 years (COPD patients mean 13.3, SD 4.9 months, and restrictive lung disease mean 11.2, SD 8.5 months) has been one tablet Hycodan four times a day. Four patients take between 6 and 8 tablets per day. Neither subjective evidence of tolerance nor objective evidence of respiratory acidosis has been found in these patients. However, it should be reiterated that patients with lung disease differ in their ventilatory response to narcotics and the acute response to the drug should be tested before recommending long-term therapy. Finally, controlled double-blind studies of narcotics in the relief of dyspnea should be carried out to ascertain the validity of this approach.

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THE MOUNT SINAI JOURNAL OF MEDICINE

VOLUME 51 NUMBER 3 JUNE 1984

CONTENTS

Lita Annenberg Hazen Award 1983 227

The Role of Pharmacotherapy in Secondary Prevention of Myocardial Infarction and Death *Richard Gorlin, M.D., and Valentin Fuster, M.D.* 229

Diagnosis-Related Groups: Physician and Abstractor Reliability and Financial Significance of Errors *Andrew B. Bindman, A.B., Lawrence F. Eichenfield, B.A., and Stephen A. Geller, M.D.* 237

Anthracycline Antibiotics as Cellular Disruptors: Insights into Anthracycline-Induced Cardiomyopathy *William Lewis, M.D., Sarah E. Amelar, B.A., and Saul Puszkin, Ph.D.* 246

Complementary Effect of Cholecystokinin-Octapeptide and Soy Flour Treatment in Chronic Pancreatitis *Akos Pap, M.D., Ph.D., Zoltan Berger, M.D., and Vince Varro, M.D., Sc.D.* 254

Prospects in Medical Care: Physicians, Patients, Practice *Eli Ginzberg, Ph.D.* 258

Effects of Antithymocyte Serum on Cardiac Allograft Survival in Thymectomized-Splenectomized Rats *D. Racelis, B.S., G. P. Martinelli, Ph.D., D.Sc., and Harry Schanzer, M.D.* 262

Contents continued inside

THE MOUNT SINAI JOURNAL OF MEDICINE

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Volume 51
Number 3
June 1984

CONTENTS *continued*

Feline Genitourinary and Systemic Circulatory Changes due to a Vasopressin Hormonogen *Robert J. Greenstein, M.D., and David A. Dreiling, M.D.* 268

Use of One-Piece Shunting System in Adults *Martin H. Savitz, M.D., and S. Sheldon Katz, M.D.* 271

Leishmaniasis *Harvey Levitan, M.D., Irwin Kantor, M.D., Lawrence J. Levitan, M.D., and Mark Levitan, B.A.* 274

Tuberculosis Infection in Mount Sinai Medical Students: 1974–1982 *Robert S. Weinstein, M.D., Joan Oshins, R.N., and Henry S. Sacks, Ph.D., M.D.* 283

Splenectomy for Chronic Idiopathic Thrombocytopenic Purpura *Barry Salky, M.D., George Katsoyannis, Arthur H. Aufses, Jr., M.D., and Isadore Kreel, M.D.* 287

CASE REPORTS

Harlequin Fetus in Twins *Austin Abramson, M.D., Rhoda Sperling, M.D., and Jasmin Moshirpur, M.D.* 290

Veno-Occlusive Syndrome of the Liver in an Alcoholic Man *Seraphim Rimarenko, M.D., and Jaishree Jagirdar, M.D.* 292

Purulent Pericarditis Caused by *Streptococcus anginosus-constellatus* *Robert F. Reder, M.D., Harold Raucher, M.D., Michael Cesa, M.D., and Bruce P. Mindich, M.D.* 295

An Association of Parotid Carcinoma with Von Hippel-Lindau Syndrome *Lorraine Nardi, M.D., and Shlomo Constantini, M.D.* 298

STUDENT'S CORNER *Howard Levin, M.S., Editor*

Breast Cancer: Risk Factors and Etiology *Marta Rico, Ph.D.* 300

Postsurgical ARDS: Case Report *Mark A. Epstein, A.B., and Anthony J. Stern, A.B.* 305

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Index to Advertisers

Allied/Regency Medical Laboratories	cover 3
Blue Cross and Blue Shield of Greater New York	cover 4

Robert J. Lefkowitz, MD (right), investigator, Howard Hughes Medical Institute and James B. Duke professor of medicine at Duke University, receiving the fifth annual Lita Annenberg Hazen Award for Excellence in Clinical Research on November 9, 1983 in New York City. At the podium with the recipient are Mrs. Hazen, Mount Sinai trustee, and Thomas C. Chalmers, M.D., chairman of the award committee and distinguished service professor and director, Clinical Trials Unit, Mount Sinai School of Medicine, and president and dean emeritus of Mount Sinai Medical Center. Dr. Lefkowitz developed the first radioligand binding techniques. He received the award for his continuing body of work on receptor-ligand binding.

Lita Annenberg Hazen Award 1983

Early in this century, researchers began to suspect that discrete cellular components were responsible for tightly binding drugs and other chemicals to target tissues. Two clues led them to believe this. One was that hormones and drugs are effective even at minute concentrations. Their potency per quantity administered is so great that it seemed they must interact with some specific structure of the cell. Second, these chemicals work with great specificity. A given receptor will bind with only one or a very few ligands. Minor alterations of a drug or hormone molecule can render it inactive or change the cell's response.

The nature of these sites remained unknown until the development of modern biochemical techniques. Dr. Lefkowitz made a key breakthrough in the study of receptors in 1968. As a fellow under the direction of Dr. Jesse Roth at the National Institutes of Health, he reasoned that it should be possible to study receptors directly.

Dr. Lefkowitz succeeded in attaching a radioactive isotope to a hormone ligand and letting the ligand carry the label to the appropriate receptor. He used ACTH, a hormone that stimulates the adrenal cortex to produce other hormones, and labeled it with radioactive iodine (^{125}I). This ACTH analog was incubated with special preparations derived from the cell membrane. Some of the radioligand then "stuck" to the receptors and could be separated from the molecules, which remained free-floating. The amount of radioligand bound turned out to be a function of the receptor concentration.

This invaluable technique is being used to study adrenergic receptors, receptors for insulin that regulate blood sugar levels and diabetes, and those associated with hypercholesterolemia (a genetic receptor disorder characterized by high serum cholesterol levels). More generally, the development of radioligand binding techniques has changed scientists' understanding of what receptors are and how they are regulated.

Until recently, scientists compared the relationship between receptor and ligand to a lock and a key: The receptor "lock" could only be activated by a ligand "key" with a specific molecular shape. One of the most important insights to emerge from direct binding studies is that these receptor locks are neither fixed nor stable. Instead, they are continuously turning, twisting, closing, opening, moving into the cell, and altering their accessibility. Receptors are influenced and transformed not only by drugs and hormones, but also by a variety of human disease states.

The clinical implications of the ever-changing nature of receptors are extensive. One of the most immediate is in providing a means to understand the phenomenon of drug tolerance or desensitization. Studies conducted by Dr. Lefkowitz and his colleagues in the mid-1970s using the radioligand approach yielded the first direct evidence that drug tolerance is caused by a change in receptor binding ability. These studies explain how changes in receptor behavior affect the function of beta-adrenergic drugs. And this provides the knowledge needed to design strategies that will combat tolerance and increase the effectiveness of drugs. To date, Dr. Lefkowitz has described several mechanisms that regulate receptors.

Down-regulation. Dr. Lefkowitz has detected a decrease in receptor number on the surface of the cell as the concentration of agonist chemicals increases—"down-regulation." When agonists are present, receptors appear to move inward from the surface of the cell. As a result, fewer functional receptors are present on the surface to bind with drugs. When the agonist is removed or no longer surrounds the cell, the "hidden" receptors return to the cell surface and resume normal function. Down-regulation affects clinical care, for example in treating asthma with adrenaline or similar bronchodilators and the use of tricyclic antidepressants.

Drugs are not the only agents that cause down-regulation. The aging process, for example, may be associated with lower responsivity to adrenergic therapy. Researchers have found that in rat brains the number of beta receptors on cells decreases with age. In addition, the ability of agonists to alter receptor number is also reduced. These changes may affect the ultimate success of adrenergic therapy.

Up-regulation. Dr. Lefkowitz has also described "up-regulation" of receptors (an increase in receptor number, or density) which may occur when cells are exposed to antagonists. This behavior might help explain the mechanism of unstable angina pectoris in patients rapidly withdrawn from propranolol therapy. Experiments performed in the laboratory of Dr. Lefkowitz and others suggest that this withdrawal syndrome could represent a state of beta-adrenergic hypersensitivity associated with an increase in the number of beta-adrenergic receptors.

Regulation of Receptor Coupling. Normally, binding of receptor to hormone does not by itself produce a physiological reaction. Instead, it initiates a cascade of biological events that culminate in the response. The actual binding triggers a molecular change in the receptor, which is then able to couple with other proteins in the cell membrane. If the receptor is made less able to bind stably to the regulatory protein, the whole chain of events leading to a physiological response may be halted. Conversely, if efficiency of coupling is enhanced, the physiological response is augmented. Recent discoveries in Dr. Lefkowitz's laboratory are uncovering how regulators of the structure of the receptors by phosphorylation might control coupling.

New knowledge is certain to proliferate. The task that interests Dr. Lefkowitz most is deciphering the exact sequence of steps between receptor-ligand binding and physiological response. "We've figured out a number of these steps in the last 10 years," he says. "This is the key to really understanding what a cell is doing. And we have to understand that before we can change it."

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The Role of Pharmacotherapy in Secondary Prevention of Myocardial Infarction and Death

RICHARD GORLIN, M.D., AND VALENTIN FUSTER, M.D.

Abstract

Following myocardial infarction the risk of reinfarction and death is greatest in the first months and through the first year. Several studies have shown beta blocker therapy to reduce mortality and reinfarction significantly during this period, provided therapy is begun early. The favorable outcome is unaffected by age, sex, race, number of prior infarcts, presence of complications, or location of the myocardial infarction. Neither β_1 or β_2 activity, nor intrinsic sympathetic activity, nor membrane stabilizing activity correlate with these positive results. It is important, however, that beta blockade be achieved.

Platelet modifying drugs tested in clinical trials are dipyridamole, sulfinpyrazone, and aspirin. In the Persantine–Aspirin Reinfarction Study, treatment with aspirin alone and with aspirin in combination with dipyridamole (Persantine) showed significant results in favor of treatment, particularly when begun before six months following the index infarction. Most studies of aspirin therapy alone indicate a favorable but statistically insignificant trend in the postinfarction period; however, in patients with unstable angina, short-term therapy with aspirin appears to be of significant benefit in primary prevention of myocardial infarction. The results of sulfinpyrazone studies have been confusing, one study showing a favorable trend in mortality rates without reduction in reinfarction, another showing reduction in the reinfarction rate but not mortality.

At this point, beta blockers have been demonstrated to be effective; the platelet modifiers seem to have a favorable effect overall that is encouraging but not conclusive.

Every day in the United States some 4,000 people suffer heart attacks, adding up to 1.5 million heart attacks a year. And for those who survive, the period which immediately follows, extending perhaps up to the end of the first year, is a time of unusually high risk of another and more serious attack.

However, an increasing number of interventions have now become available that are believed to have a favorable impact on both death and prevention of a second or even a third infarction. This review sums up the evidence now at hand primarily concerning two classes of drugs: first, the beta blockers, which have been called "one of those infrequent advances that revolutionize the practice of medicine" (1), and second, the platelet-inhibiting agents. We review briefly the status of this latter class of drug as a prototype for another approach to secondary prevention.

The range of interventions thought to contribute to survival following myocardial infarction can be divided into two groups: interventions which have some favorable impact, and those for which the impact, however encouraging, must still be considered unsubstantiated. Interventions that all appear to have a positive impact on mortality (2–6) are

- cessation of smoking
- control of hypertension with beta blockers
- beta blocker therapy for angina
- use of platelet-inhibitor agents
- selective use of anticoagulants

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Among those interventions for which evidence of benefit is uncertain are

- exercise programs
- lipid control
- modification of behavior patterns

It seems that for every paper showing a favorable impact of exercise on mortality or reinfarction, there is a counter claim denying benefit. This lack of clarity may be due at least in part to the problem Naughton has noted: "Of all forms of clinical trials, an exercise intervention study is among the most complicated and difficult to conduct" (7). Trial results he reported do not militate against the value of exercise, but neither do they establish a case for it.

There is as yet no evidence that lipid control by reduction of cholesterol or alteration in lipoprotein levels is effective in secondary prevention. Finally, there is no hard evidence to date that modifying behavior patterns can be accomplished or does have an effect on reinfarction and death (8).

Beta Blockers

Some of the questions on the use of beta blockers following myocardial infarction to which we want answers are

- Are the data persuasive?
- Do we treat all patients, or do we treat selectively?
- Which beta blocker should be given?
- When should beta blockers be begun after myocardial infarction?
- Can we extrapolate from the data usefully for the patient who has not had a clinical myocardial infarction, yet has ischemic heart disease?

Persuasiveness of Clinical Trial Data. A good starting point from which to consider the evolution of beta blocker therapy is the Multicentre International Study with the agent practolol (9). Practolol was a derivative of propranolol, with major cardioselective properties. Unfortunately, the drug also had such toxicity for the eye and produced such fibroblastic complications that it was withdrawn in England and was never used in the United States. In a clinical trial organized in Great Britain in the early 1970s, some 3,000 patients in several hospitals were randomized either to practolol at a dose of 400 mg or to placebo. The study showed a significant reduction in cardiac deaths in the treated group as compared with placebo, and a borderline reduction in the frequency of myocardial reinfarction (Table 1). The number of deaths among patients withdrawn from the drug and still followed equalled the number of deaths among patients withdrawn from placebo. So this important study did suggest a possible beneficial effect of beta blockers following myocardial infarction.

TABLE 1
Practolol (400 mg q.d.) Double-Blind Trial for One Year following Acute MI (3,038 patients)

	Practolol	Placebo	*p*
Cardiac deaths	47	73	<.02
Nonfatal reinfarction	69	89	<.10
All cardiac events	116	162	<.01
Noncardiac deaths	5	3	—
Cardiac deaths after withdrawal	36	37	—
Noncardiac deaths after withdrawal	6	4	—

Reprinted with permission from A Multicentre International Study. Improvement in prognosis of myocardial infarction by long-term beta-adrenoreceptor blockade using practolol. Br Med J 1975; 3:737.

A brief three-month trial of the cardioselective agent metoprolol (10) showed a significant difference in mortality between the group on placebo and the group given the drug within 12 hours of hospital admission and maintained on it for 90 days (Fig. 1). The difference between the mortality rates was evident within days or weeks following the myocardial infarction, indicating the extreme importance of beginning beta blocker therapy at an early point after infarction.

A study by Hansteen and coworkers in Norway comparing propranolol with placebo also indicated the advantage of early beta blocker therapy following myocardial infarction (11). In the course of one year this study found the major impact of beta blocker on the rate of sudden cardiac

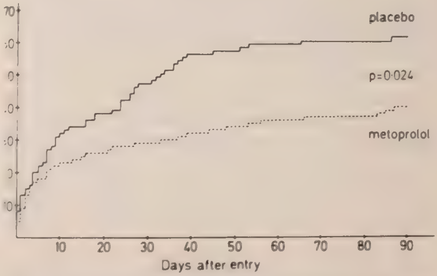

FIG. 1. Cumulative number of deaths in all patients randomly allocated to treatment with metoprolol and placebo; *p* value is calculated according to Mantel-Haenszel. Reprinted with permission from Hjalmarson et al. Effect on mortality of metoprolol in acute myocardial infarction. Lancet 1981:1:825.

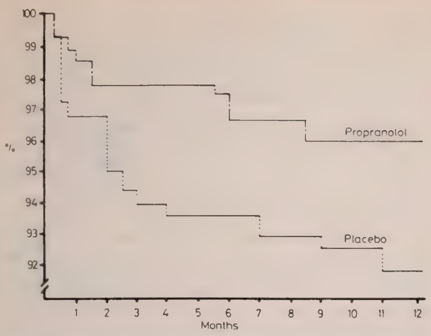

FIG. 2. Life table for cumulated sudden cardiac death rate (intention to treat). Reprinted with permission from Hansteen et al. Br Med J 1982; 284:158.

death to be in the early months of the trial. This suggested that the beta blocker had antifibrillatory actions, particularly in the immediate postinfarction period. The biggest impact was within the first three months, after which the survival curves tended to parallel one another (Fig. 2).

In a study of timolol in Norway (12), a virtual majority of the hospitals in this small country undertook a cooperative trial, and thousands of patients who had survived a heart attack were followed for more than three years. Cumulative mortality when the drug was given within the first few days after myocardial infarction was significantly less than with placebo (Fig. 3). Myocardial reinfarction was also less in the early period, although beyond the two-year point the curves are much alike. These findings serve to emphasize again that the risk is greatest during the first months and continues primarily through the first year after infarction.

In the Beta Blocker Heart Attack Trial (BHAT), sponsored by the National Institutes of Health, nearly 4,000 patients were randomized to placebo or to propranolol in doses varying from 180 to 240 mg (13). The survival curves diverge early in the first year, then maintain the difference, although at a similar slope, over a 30-month period. Total mortality over the first two years was 9.5%; in the propranolol group, mortality was 7% (Fig. 4). Because of the large numbers involved, the difference is statistically significant; mortality in the treated group was about 26% lower than in the untreated (placebo) group. The rate of sudden death among treated patients was 3.3%, whereas among patients receiving placebo that rate was 4.6%—again, a significant difference because of the sample size. In addition, the BHAT trial demonstrated reduction in reinfarction rate with beta blocker therapy in the postinfarction period.

Surprisingly, many of these recent studies reveal a relatively low risk of mortality in the placebo groups. This low risk was unanticipated and therefore unplanned for in the study designs. In fact, a recent decline in mortality in the United States is well documented (14). This raises the question of whether something is happening to the disease that we cannot yet define. Are the general changes in diet and life-style that physicians recommend to patients with coronary disease having an impact on mortality? Is coronary

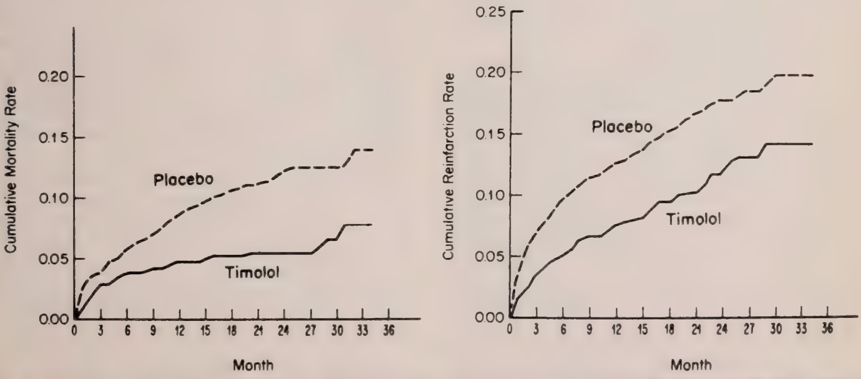

FIG. 3. Life-table cumulated rates of sudden cardiac death (left) and first reinfarction (right) during administration of timolol or within 28 days of the last dose. Reprinted with permission from The Norwegian Study Group. N Engl J Med 1981; 304:806, 807.

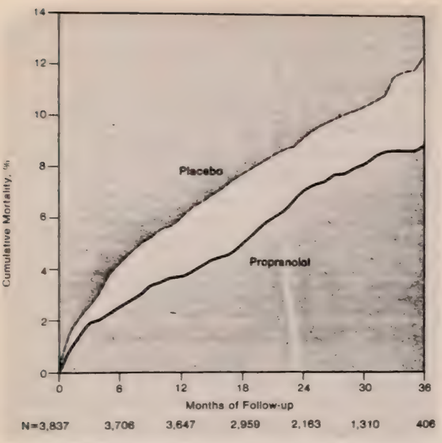

FIG. 4. Life table cumulative mortality curves for groups receiving propranolol hydrochloride and placebo. N indicates total number of patients followed through each time point. Reprinted with permission from Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction. JAMA 1982; 247:1709. Copyright 1982, American Medical Association.

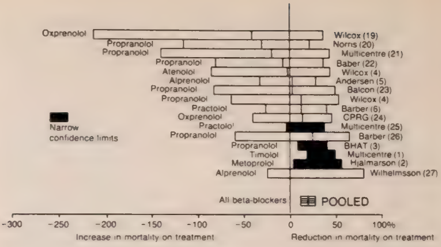

FIG. 5. Effect of beta-blockers on postinfarction mortality. Difference in mortality expressed as a percentage of control rate in 16 controlled trials of beta blockers; 95% confidence limits based on odds ratio consideration. Reprinted with permission from Lewis et al. A statistical appraisal of post-infarction beta-blocker trials. In: Prevention of myocardial reinfarction: what is the role of beta-blockers? Primary Cardiology Supplement 1982; 1.

atherosclerotic disease itself changing in some way? Certainly the biostatisticians who designed the studies projected a much higher mortality rate for the placebo groups (14). In the BHAT study, the placebo group had an average mortality of 6% at one year, about half the predicted rate. Something changed between the time these studies were designed and the time they were conducted, something that has lowered the overall mortality for coronary heart disease in most of Western society, at least in the phase immediately following infarction.

Yet, despite the lower-than-expected mortality rate among patients receiving placebo, the difference between the treated and the placebo groups was still significant. Variables such as population, country, study design, and drug may have affected the magnitude of what is a uniformly favorable response. The narrower the statistical confidence limits of a study, the more meaningful it is. Comparing all trials to date of beta blockers reveals that the practolol, BHAT, timolol, and metoprolol trials have the narrowest confidence limits, and each of these trials resulted in 25%–40% reductions in mortality (Fig. 5). Indeed, the general preponderance of evidence tends toward reduction in mortality with beta blocker therapy.

Who Should Receive Beta Blockers? Should patients be treated selectively? Should we substratify for age, sex, race, or type or severity of myocardial infarction in selecting therapy?

In the BHAT study, the outcome for all age, sex, and race subsets was significantly lower mortality in the treated group compared to the placebo group (Table 2). Even when the degree of intrinsic risk is analyzed, the difference between propranolol and placebo is maintained.

Patients entering the BHAT study were categorized by risk group (13). Risk group I patients had more than one previous myocardial infarction. Risk group II patients had a first infarct complicated by failure, arrhythmias, shock, or other factors. Risk group III patients had an uncomplicated course. Despite the expected differences in mortality between these three risk groups, there was a difference in mortality within each group between drug and placebo (Table 2).

Patients in the BHAT trial were also classified for location of infarct as a third subset (Table 2). The 1975 practolol study (9) had indicated that possibly only anterior infarctions benefitted from therapy. The BHAT trial results revealed that although anterior infarct entails a greater risk than any other infarct site, all infarcts were favorably affected in terms of the ultimate outcome. So none of the factors examined—age, sex, race, risk group, and location of infarct—appears to have influenced the consistent difference between placebo and propranolol on outcome. Perhaps patients at higher risk of sudden death—those with decreased ejection fraction, rhythm abnormalities on Holter monitoring or abnormal treadmill stress test—might be the ones to receive the most benefit from beta blockers; this hypothesis, however, remains to be tested.

TABLE 2
Percent Total Mortality in BHAT Trial
(Average 24-month Follow-up)

	Propranolol	Placebo
By clinical characteristic		
Age 30–59	5.9	7.1
60–69	9.6	14.4
Sex male	7.0	9.3
female	7.1	10.9
Race white	6.7	9.0
black	11.0	15.2
By risk group		
Risk Group I (more than 1 MI)	13.5	16.9
Risk Group II (complicated single infarct)	7.8	11.4
Risk Group III (single infarct)	5.2	7.1
By infarct location		
Anterior	8.4	11.7
All other sites	6.3	8.3

Adapted from Beta-Blocker Heart Attack Trial Research Group. A randomized trial of propranolol in patients with acute myocardial infarction: I. Mortality results. JAMA 1982; 247:1707–1714.

TABLE 3
Properties of Beta-Blockers Shown to Reduce Mortality in Myocardial Infarction

	B_1	B_2	ISA*	MSA†
Alprenolol	+	+	+	+
Practolol	+	–	+	+
Timolol	+	+	–	–
Metoprolol	+	–	–	–
Propranolol	+	+	–	+

* ISA: Intrinsic sympathomimetic activity
† MSA: Membrane stabilizing activity
From Brian N. C. Prichard, personal communication, 1982.

Which Beta Blocker? Among the well-tested beta blockers, does it matter which is used? Four features of beta blocking agents are B_1 and B_2 activity, intrinsic sympathetic activity, and membrane-stabilizing or quinidine-like action. There seems to be no correlation between any of these features and the favorable actions of alprenolol, practolol, timolol, metoprolol, or propranolol (Table 3). Hence any of these blockers appears to be suitable for arriving at the results we seek. One principle seems self-evident: the dose given should produce beta adrenergic blockade to assure the intended effect.

When to Begin Beta Blockers. A number of clinical trials purport to show reduced arrhythmias, infarct size, and mortality when beta blockers are given intravenously on the patient's entry to hospital with a myocardial infarction (13). These results remain to be proved as established therapy, however. What is clear is that except for classical contraindications such as heart failure or heart block, beta blockers can safely be given during acute myocardial infarction.

The wisest course may be to wait until the time of discharge, perform a limited stress test (or gated blood pool scan) and then initiate beta blocker therapy.

A recently published British trial has led to some questions and confusion about the agent oxprenolol (15). This agent, which has some intrinsic sympathetic activity, was used as a possible agent to prevent myocardial reinfarction. However, patients entered the study at different times following myocardial infarction. When patients were entered within the first few months after the infarction, the mortality statistics are consistent with prior data. The patients taking oxprenolol early had a very different mortality curve from the placebo group up to six years after myocardial infarction (Fig. 6, left). Yet the investigators also randomized patients into the trial a full year after myocardial infarction, a time when patients might be considered to be in the "safe" period. Fig. 6 (right) illustrates a paradox: the patients started on oxprenolol did poorly, while those on placebo did well! There are some possible conclusions to be drawn. First, perhaps all beta blockers are not equally protective. Second, only early administration after myocardial infarction may be cardioprotective. Third, late administration, after the first 12 months, may have an adverse effect. One fact revealed only in the body of the report was that most of the patients started late on the drug had stopped taking the drug long before mortality occurred. The significance of these confounding results is unknown.

Clinical Indications for Beta Blockers. Beta blockers are clearly indicated for patients with continuing angina, hypertension, and certain arrhythmias. They are probably indicated for *every* patient judged to be at high risk; they may well be indicated for *any* patient who has no specific contraindication, such as heart failure, heart block, or asthma. We do not know, however, if these results can be extrapolated to the patient with angina who has not sustained an acute myocardial infarction. As the period from acute myocardial infarction to beginning of therapy increases, results become more equivocal, suggesting that the protective effects on chronic ischemic heart disease may be relatively small.

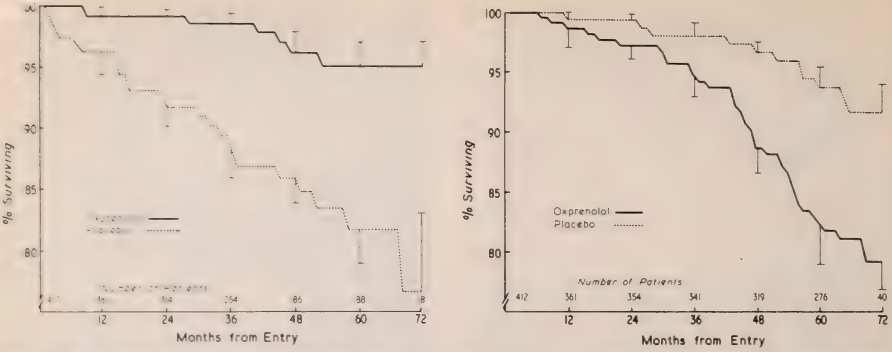

FIG. 6. Life-table cumulative survival curves for patients (**left**) entered within four months of infarction and (**right**) entered more than 12 months after infarction. Values are expressed as means ± SE (bars). Reprinted with permission from Taylor et al. A long-term prevention study with oxprenolol in coronary heart disease. N Engl J Med 1982; 307:1297.

Platelet Inhibitor Agents

Platelet Modifying Agents. The platelet modifying drugs tested in clinical trials are dipyridamole, sulfinpyrazone, and aspirin.

The findings of the Persantine–Aspirin Reinfarction Study (PARIS trial) are of greatest interest (16). Persantine (dipyridamole) and aspirin were tested in 2,026 patients randomized to either Persantine three times a day plus aspirin (324 mg three times a day), or to aspirin (324 mg three times a day) alone, or to placebo alone. The placebo group had a 10% myocardial infarction rate, whereas reduced rates were found for patients treated with aspirin alone and with aspirin and Persantine in combination (Fig. 7).

Early use of the beta blockers after infarct influences effectiveness. In the PARIS trial, when treatment began more than six months after myocardial infarction the rates of coronary death over a 44-month period were no different for patients treated with placebo, with aspirin, and with Persantine plus aspirin (Fig. 8). When treatment was begun before six months after the index infarction, there was a marked difference between placebo and the two treatment groups, the best results within the first two years of followup being in the Persantine plus aspirin group. There is a clearcut major difference in favor of starting the drugs early.

Table 4 restates the dangers of the early postinfarction period in the starkest terms. The number of deaths for patients starting therapy more than six months after infarction was almost identical to the number of deaths among those starting therapy less than six months afterward—except for patients started on placebo less than six months after myocardial infarction. Their mortality rate was almost double that for patients receiving aspirin or Persantine plus aspirin, or surviving six months irrespective of therapy. (The PARIS I study was substratified after the trial was in progress with respect to time post myocardial infarction for start of therapy. Therefore the results are not statistically as solid as one would like. Consequently, a second prospective time trial has been initiated.)

In addition to the PARIS study, seven other major trials of platelet inhibitors were conducted

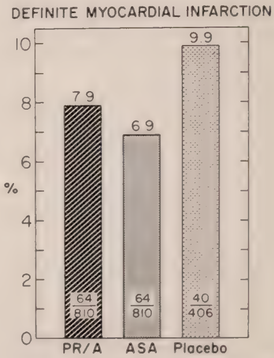

FIG. 7. Aspirin-Placebo Cox adjusted Z-value = 2.11. Adapted from The Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. Circulation 1980; 62:449–461.

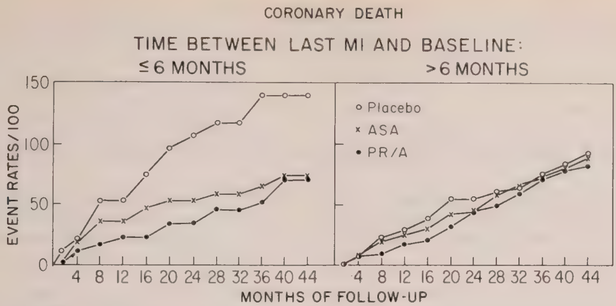

FIG. 8. Cumulative event rates for patients according to time between last myocardial infarction (MI) and baseline. Reprinted by permission of the American Heart Association, Inc., from The Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. Circulation 1980; 62:458.

between 1974 and 1982, involving more than 14,000 patients (including PARIS) and with short-term reinfarction or mortality as endpoints (17–23). Follow-up ranged from one year to almost four years.

In the five trials of aspirin alone (dosage range, 300–1500 mg per day), a favorable trend in rates of coronary events among treated patients appears in all but one study, where no benefit or trend was in evidence (16–18, 20, 21). Perhaps coincidentally, this was also the study with the longest interval between myocardial infarction and entry into the trial, a mean period of 25 months.

The two sulfinpyrazone trials (22, 23) produced mixed results. In one there was a favorable trend in the mortality rates but no reduction in reinfarction (22). The other trial showed no reduction in mortality but a significant lowering of the reinfarction rate from 9% among placebo patients to 4% in the treated group (23). The reasons for such diametrically opposite results are not yet known.

The evidence on platelet modifiers or inhibitors for the prevention of reinfarction thus far is suggestive rather than conclusive; there seems to be an overall favorable trend, but at this stage it should probably be regarded as only a trend, albeit an encouraging one (24).

TABLE 4
Percent Dead by Time Since Qualifying Myocardial Infarction

Time since qualifying event	Persantine + aspirin	Aspirin	Placebo
<6 months	10.6	9.8	18.9
>6 months	10.8	10.7	10.9

Adapted from The Persantine-Aspirin Reinfarction Study Research Group. Persantine and aspirin in coronary heart disease. Circulation 1980; 62:449–461.

Regarding primary prevention of myocardial infarction in patients with unstable angina, short-term therapy with aspirin (325 mg/d) appears to be of significant benefit (25); nevertheless this needs to be confirmed with further trials.

Summary

The weight of the evidence is in favor of the beta blockers and certain platelet modifiers as playing effective roles in the prevention of myocardial reinfarction. Further, there is no clearcut indication that any one beta blocker is better than any other among the agents which have been given the most stringent trials. The overall role and indications for the use of platelet inhibitor drugs in patients with coronary artery disease (with or without myocardial infarction) is likely to be better clarified within the next five years.

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Diagnosis-Related Groups: Physician and Abstractor Reliability and Financial Significance of Errors

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Abstract

The introduction in 1983 of Medicare's prospective payment program based on diagnosis-related groups (DRGs) presupposes that face-sheet abstractions of discharge data are reliable. In a retrospective review of charts of 43 patients with the primary discharge diagnosis of chronic obstructive pulmonary disease, 42% of reabstracted charts had a medically justifiable change in primary diagnosis. In addition, there was a 33% change in DRG classification which increased the hospital's potential reimbursement. Medical-record abstractors made additions to physician-completed face sheets in 56% of the cases. Thus, this study emphasizes the importance of physician documentation of diagnoses in medical records, and examines the potential effect of DRG assignment on reimbursement.

In 1982, health care expenditures increased at almost three times the national inflation rate. From the onset of the entitlement programs in the 1960s to September 1983, hospital care costs have risen from $13.9 billion in 1965, to $99.6 billion in 1980, an increase of more than 600%. The Office of Management and Budget has estimated that, in 1983, Medicare alone will account for a federal government expense of $46.9 billion, with projections of doubling of costs by 1987 if present trends continue. In addition, it is projected that the Medicare trust fund will be insolvent by the late 1980s if the current rate of expenditures continues.

Legislation passed in March 1983 amending the Social Security Act altered Medicare's system of reimbursement to hospitals. Medicare, which originally reimbursed hospitals retrospectively according to their itemized lists of costs for treating eligible patients, has shifted to a prospective approach in which payment is based on the patient's diagnosis and not on actual costs for care. This was implemented nationwide on October 1, 1983, with certain exceptions (1). The new plan bases hospital cost ceilings on cost per case and attempts to associate medical services and their costs with the diagnosis of the patient. These radical modifications of the health care reimbursement system could be considered the inevitable result of the high cost of medical care, which is currently at approximately 10 percent of the gross national product. These costs are viewed by the public as excessive.

One of the aims of this prospective-reimbursement system is to allocate more money for more difficult cases, and less money for simple ones. This might have been pursued as a policy under the system of reimbursement for itemized costs; however, that plan provided no way, other than an inefficient peer review system, to determine if accumulated costs were appropriate for any one case. For example, the costs of caring for any patient with a given disease can vary greatly from institution to institution. By setting fixed prices that vary with disease complexity, as defined by government-estimated consumption of hospital

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resources, the government hopes to recognize different payment needs for different types of cases, to encourage hospitals to be more cost efficient in their care of patients, and to contain costs.

Variables in Federal DRG System. In order to systematically appraise Medicare's appropriate contribution to the cost of hospital care, Congress chose cost classification by diagnosis-related groups (DRGs). A DRG is a grouping of patients defined by a number of variables. These may be age, sex, primary diagnosis, presence or absence of a preexistent disorder, presence or absence of complications, performance or nonperformance of operating-room procedure; in one such system, the disposition of the patient is a factor.

Each DRG includes a heterogeneous assortment of diagnoses that are united in one group because they are thought to incur similar expenses. Procedures are defined as DRG-significant if they are performed in an operating room. DRG assignment is based on a ranking system in which operating-room procedures take precedence over medical diagnoses. Patients who do not undergo an operating-room procedure are classified in the medical portion of the system, separated according to diagnoses. Further stratification is based on age or "substantial comorbidity or complication," defined as a condition which is likely to increase the length of hospital stay by at least one day in 75% of all cases. The six major variables listed above reduce over 10,000 diagnoses identified in the ninth revision of the International Classification of Diseases (ICD-9) (2), currently in use in medical records departments, into 467 medically meaningful and statistically homogeneous groups. All patients in the same DRG should have similar hospital resource needs, as estimated by length of stay in the hospital, and these needs may be different from those for patients in other DRGs. Rates can be assigned to each DRG by averaging the cost of treating patients within each group at different hospitals. Adjustments can be made depending on whether the treating institution is rural or urban, or a teaching or nonteaching facility.

For a small percentage of patients, the hospital course will differ markedly from the expected length of hospital stay. Any patient who for legitimate medical reasons falls outside the normal distribution is considered an "outlier" whose reimbursement is determined by other means. Although DRGs were not originally designed as a case-mix measuring tool, and were not part of a reimbursement scheme, they will now be used to set payment rates.

Cost Containment Shift to Hospitals. When DRGs are used as part of a prospective payment plan, the responsibility of cost containment is shifted from the government to health care providers, particularly hospitals. Costs which exceed those based on a patient's diagnosis must be covered either by the hospital, the patient, or some party other than Medicare, since the government will not reimburse above the DRG limits. In addition, hospitals are offered the incentive of "earning" up to 50% of the difference between actual costs and the DRG ceiling whenever they keep costs below the DRG limit. The DRG system was described by Richard Schweiker, former secretary of the Department of Health and Human Services, as having the ability to reward hospitals for the efficient delivery of care (3). However, this plan provides few controls to guarantee the quality of medical care other than a poorly defined proposal to improve peer review. Iglehart writes that "the new payment approach will indeed provide institutions with an incentive to economize" (4). He also notes that, "looked at another way, hospitals also will have a new incentive to underserve patients." The Department of Health and Human Services has avoided this issue by indicating that it has no role in telling physicians how to practice: "We believe that any actions the federal government takes with respect to bringing about efficient economic behavior in hospitals should create incentives for such behavior, but should interfere as little as possible in the actual methods used to achieve economic efficiency" (5).

Potential DRG Problems. Under the DRG system, hospitals will either have to improve their cost efficiency in those services which exceed government reimbursement limits or stop offering such services. While physicians' private fees are not affected by the current prospective payment plan, discussion is already under way to incorporate these costs into a more complete program.

Even without an immediate change in the system of private fees, physicians will be the target of a number of forces redirecting their behavior. In Iglehart's view, a prospective payment plan which emphasizes cost efficiency rather than quality control may cause large shifts in health dollars, a decrease in Medicare recipients' hospital access, and a fundamental change in the physician's relationship with colleagues, the hospital administration, and the medical-records department (4). Physicians are traditionally concerned with doing the most they can to help their patients, and have the added incentive of being able to charge a greater fee for increased service. Hospital administrators, who in the past encouraged utilization of hospital resources, will now be

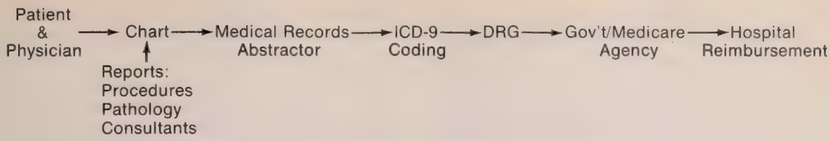

FIG. 1. Flow of information leading to hospital compensation.

preoccupied with lowering costs and will put pressure on physicians to do less for patients. Administrators may create competition among physicians because of the decreased allotment of funds for patient care, laboratory work, and new equipment. Finally, there is potential for strain between physicians and medical-record personnel, who may be required to maximize profits by pressuring physicians for prompt, complete documents which emphasize diagnostic points based more on potential reimbursement than on medical judgment.

Importance of Face Sheet and Chart. Reimbursement depends upon the diagnosis and other DRG-relevant material recorded on the face sheet of the patient's chart. The face-sheet summary of primary discharge diagnosis, secondary diagnoses, surgical and operative procedures, and other diagnostic procedures is a single-page compilation of this information, now used for medical-records billing and cataloging of hospital casework. Information on the face sheet will have to be specific, complete, and clear in order to assure that monies are not lost in the course of the translation of pertinent medical data into hospital compensation (Fig. 1).

Patient-physician interaction requires that the physician document information relevant to the clinical course of the patient. The clinical chart serves as the medical body of knowledge about each patient and includes consultations, records of procedures, and laboratory reports. When the patient is discharged, the physician adds a case summary to the chart and completes the face sheet. The summary is not always written promptly. The face sheet, on the other hand, is generally completed just before the patient leaves the hospital. Medical-records personnel must thoroughly review the medical record for information which belongs on the face sheet, in order to confirm or augment the physician's diagnoses. For each diagnosis, they add the appropriate ICD-9 code (2). In this way, the coded information can then be entered into a computer, along with the patient's age, to yield a DRG for that patient which can be forwarded to the appropriate government office for eventual reimbursement.

We designed a study to determine how physicians' reporting of medical information affects face-sheet abstraction and coding. In anticipation of the impending implementation of the Medicare prospective payment plan, we wanted to analyze how physicians' reporting behavior, as determined by comparing data in the complete clinical chart with the diagnoses on the face sheet, could affect DRGs and subsequent reimbursement to the hospital.

Methods

We retrospectively surveyed medical charts for patients with the same primary diagnosis during a one-year period.

Charts for all patients discharged during 1982 from The Mount Sinai Hospital with the primary discharge diagnosis of chronic obstructive pulmonary disease (COPD), specifically recorded by medical abstractors as ICD-9 Code 496, were reviewed. COPD was selected as the tracer diagnosis for this study because (a) it was suspected that the standard DRG flow scheme contains a number of codes for problems commonly associated with COPD; (b) it was thought that the number of charts for review would be appropriate for our study; and (c) COPD affects an older population likely to have medical complications and comorbidities.

A list of 53 hospital numbers for all patients with the primary discharge diagnosis of COPD was generated from the computer records. However, only 47 clinical charts were recovered; the other six were unavailable for review. Of these 47, only 43 charts, from 42 patients, satisfied the criterion of a primary diagnosis of COPD with a medical abstractor coding of ICD-9 496; 5 charts were discounted for having some other ICD-9 code.

Charts were reviewed to determine

- completeness of physician's documentation of diagnosis
- completeness of the medical-record abstraction
- validity of the discharge diagnosis

This review was carried out by examination of the face-sheet summary and the complete medical chart, as explained below.

The quality of physician reporting as it may affect DRG coding was assessed by noting the addition to the face sheet of DRG-relevant information by medical-record abstractors. DRG-relevant information is information which, in terms of the standard ICD-9 revised DRG coding scheme, could potentially change a patient's DRG classification. This definition of "DRG relevant" was used to determine how face-sheet information affects DRG assignments. This was necessary because the DRG classification for our index diagnosis, COPD, excludes many of the standard criteria used for DRG coding, including age, and substantial complication or comorbidity, and would tend to obscure documentation errors that could potentially have important fiscal ramifications in other diagnostic categories.

We recorded patient hospital number, age, and admission and discharge date. We reabstracted the entire chart to determine the primary and secondary diagnoses, the presence or absence of operating-room procedures, and the occurrence of any complications during the hospital course. Discrepancies were noted and classified according to the following scheme:

A: abstractor error (clerical error or misinterpretation of physician notes)

B: physician error (failure of adequate or appropriate documentation)

C: disease overlap error (error due to a disease falling into more than one category)

D: chart incomplete (information possibly relevant to diagnosis or DRG obviously missing from the chart at the time of initial review).

Each reviewer recorded as primary those diagnoses considered more accurate or medically more justified than those listed by the abstractors. Similarly, the presence or absence of substantial complication or comorbidity, in terms of DRG definitions, was recorded. Criteria for these diagnostic changes cannot be enumerated in detail since they are based on the knowledge and experience of the reviewers.

As a means of controlling the reviewing method, all charts in which a reviewer was uncertain whether a different diagnosis was justified, or a comorbidity or complication was present, were reabstracted by a second reviewer. Any diagnostic change was discounted if either felt it was not medically justifiable.

We used diagnoses reported by physicians, by medical-records abstractors, and by our reabstraction with the ICD-9 revised DRG flow charts (Fig. 2) to assign a DRG for each patient (6). The Yale ICD-9 lists of operating-room procedures were the standard for determining if cited procedures satisfied DRG criteria, and if they ranked above the medical DRG (7). Similarly, the Yale codes were used to define and grade any significant comorbidity or complication.

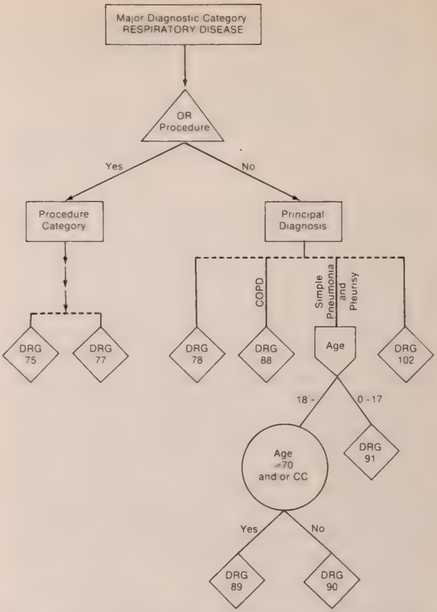

FIG. 2. Flow chart of DRG assignment. OR = operating room; CC = complication-comorbidity. Adapted from Commission on Professional and Hospital Activities. DRGs and medical records, 1983.

Dollar Reimbursement Values. Fiscal analyses were carried out to determine the potential effect on hospital reimbursement of the changes in DRG assignment made after reviewer reabstraction of the charts. New York State and The Mount Sinai Hospital were not operating under a DRG-based reimbursement system at the time of this study, and we substituted DRG-dollar values in use in a suburban New Jersey hospital. Three DRG categories had outlier status and no DRG-dollar figures because an insufficient number of cases with these DRGs had been seen in that hospital. Dollar figures for those DRGs were calculated using a DRG conversion code now under review. The code is a relative weighting of DRG reimbursement without specified value. For example, "seizures" has a .7029 weighting, as compared to the 1.966 weighting of "pleural effusion (>70 yrs, and/or CC [comorbidity or complication])," with reimbursement computed from the weighting factor multiplied by some average dollar value for that hospital or region. The average dollar value used for our calculations was the New Jersey hospital dollar value for COPD divided by its DRG conversion factor, 1.0713.

Total DRG-based reimbursement for the 43 cases was calculated for DRGs derived from medical-records abstractor evaluations of face sheets (medical-records abstractor group) and for the DRGs assigned by reviewers (reviewer group).

In a separate analysis of reviewer-abstracted information, we reassigned DRGs by comparing diagnoses for each case on the basis of maximizing reimbursement. For example, if COPD (DRG code 88) and pneumonia, >70 yrs or CC (DRG code 89) were justifiable diagnoses, DRG 89 would be assigned because pneumonia has the higher reimbursement value. Total reimbursement for the 43 cases with fiscally maximized DRGs were calculated.

Results

Primary Diagnosis. In all 43 charts examined, medical-records abstractors had assigned the primary diagnosis of chronic obstructive pulmonary disease (COPD), as per study design. In reabstracting the charts, the reviewers found 25 of the 43 primary diagnoses to be COPD, and considered 18 of 43 (42%) to have justifiably different diagnoses (Table 1). Of the 18 changed diagnoses, 5 were reclassified as congestive heart failure, 4 as pneumonia, and 9 as other single diagnoses. Analysis of the reasons for discrepancies between abstractor and reviewer diagnoses (Table 2) showed error attributable to physicians in 9 cases, to medical-records abstractors in 1 case, and to the disease overlapping DRG categories in 9 cases (1 case with more than one error).

TABLE 1

Primary Diagnoses by Reviewers, 43 Charts Originally Coded as COPD

25/43	Chronic obstructive pulmonary disease
4/43	Pneumonia
5/43	Congestive heart failure
9/43	One each: effusion; atelectasis; lung abscess; interstitial fibrosis; seizure disorder; acute myocardial infarction; ischemic cardiomyopathy; apnea; subglottic stenosis

TABLE 2

Reasons for Discrepancy in Diagnosis or DRG

	Physician Error	Abstractor Error	Disease Overlap
Change in diagnosis	9	1	9
Change in DRG	6	1	8

DRG Classification. DRGs assigned on the basis of face-sheet information supplied by medical-records abstractors included 37 of 43 charts (86%) with DRG 88 (COPD); the remaining 6 charts (14%) were assigned a DRG procedure code, which supersedes the medical DRG (Table 3). In our reviewer-reabstracted charts, the same 6 charts were assigned a DRG procedure code, but only 23 charts (53%) were given the COPD DRG code; the remaining 14 were assigned other medical DRGs (Table 4). Thus 33% (14 of 43) of charts reabstracted were assigned different DRGs, on the basis of different medically justifiable primary diagnoses. The DRG changes were due to errors by physicians in 6 cases, errors by medical abstractors in 1 case, and disease-overlap of DRG categories in 8 cases (Table 2).

Reassignment of DRGs was also based on the maximization of reimbursement, where different justifiable DRGs were possible for a given chart. Of the 14 charts with potential changes in DRGs, 10 (23%) were assigned non-COPD DRGs, while 4 (9%) remained as the COPD DRG (Table 5).

Fiscal Analysis of DRGs. Income for the three groups of DRGs in our study—the original DRG assignment, our reviewers' assignments, and our maximized-reimbursement reviewer assignment—does differ. As shown in Table 6, reimbursement for the original medical-abstractor-assigned DRGs was approximately $12,000 less than the maximized-reimbursement reviewer assignment. That is an 8.93% difference in income for the same health care.

DRG-Relevant Additions to Face Sheet. Medical records abstractors made additions to the face sheet in 25 of 43 charts (58%) (Table 7). Of these

TABLE 3

DRG Classification: Abstractor vs. Reviewer

	Abstractor	Reviewer
DRG 88 (COPD)	37/43 (86%)	23/43 (53%)
DRG procedure code	6/43 (14%)	6/43 (14%)
Other medical DRG	0/43	14/43 (33%)

TABLE 4

Reviewer DRG Assignment

No.	DRG No. and Category
23 43	88: Chronic obstructive pulmonary disease
5 43	76: Procedure code: operating room procedure on respiratory system except major chest with operating room procedure
1 43	468: Procedure code: unrelated operating room procedure given to a major diagnostic category
4 43	89: Simple pneumonia and pleurisy (70+ yrs or CC)
3 43	127: Heart failure and shock
2 43	101: Other respiratory (70+ yrs or CC)
1 43	24: Seizure and headaches (70+ yrs or CC)
1 43	85: Pleural effusion (70+ yrs or CC)
1 43	92: Interstitial lung disease (70+ yrs or CC)
1 43	121: Acute myocardial infarction (circulatory disorder with AMI and cardiovascular compromise, discharged alive)
1 43	144: Other circulatory with CC

CC = complication-comorbidity

TABLE 5

Fiscally Maximized DRG Assignment

Coded as DRG 88 (COPD)		27/43 (63%)
COPD unequivocal diagnosis	23	
Two diagnoses possible; COPD fiscally favorable	4	
Coded as other DRG		10/43 (23%)
Simple pneumonia and pleurisy	4	
Heart failure and shock	3	
Acute myocardial infarction	2	
Pleural effusion	1	
Coded as a DRG procedure code		6/43 (14%)

abstractor additions, 7 of 43 (16%) changed the comorbidity-complication status of the patient, although these changes were not reflected in the DRG assignments for COPD. Our reviewer survey showed a change in comorbidity-complication status in 3 of 43 cases (7%), attributable to information in the chart missed by physicians (twice) and medical abstractors (twice).

DRG-Relevant Information Absent from Chart. Although at least 6 months had passed between the final discharge date and the time of reviewer reabstraction, 12 charts were incomplete, lacking information potentially useful for abstractors. Of these 12 cases, 6 had no discharge summary, 2 were without pathology reports, including 1 autopsy report, 3 lacked pertinent x-ray reports, and 1 was missing the liver-spleen scan report.

Discussion

While there is a vast literature on many aspects of controlling medical costs, including a number of proposed models for modifying physicians' behavior, there is little more than editorial and speculative comment on how physicians' reporting behavior is related to cost containment. In fact, until 1977, almost 20 years after standardized formats were developed for coding and compiling medical-record abstracts, there had been no national, randomized study on the reliability of medical-record face sheets as a reflection of the chart material. The Institute of Medicine, following the lead of Hendrickson and Myers (8), and three state agencies conducted the first studies generalizable to a national population (9–13). These studies raise serious questions about the reliability of information on the face sheet, particularly with regard to diagnoses and procedures, and indicate the important role that physicians play in determining what information is coded. However, no study to date has evaluated the extent of the physician's impact. The introduction of a prospective plan means, in effect, that face-sheet information is translatable into dollars. Our study demonstrates the importance of physician documentation in medical records and the effect such documentation has on DRG assignment and reimbursement.

Primary Diagnosis and DRG Assignment. A high percentage of face sheets were justifiably changed in terms of primary diagnosis and DRG assignment. Our finding of a valid change in 42% of the charts, when comparing medical-abstractor diagnosis to reviewer diagnosis, is startling but consistent with the findings of other studies. In the 1980 Institute of Medicine follow-up study of hospital discharge data, the reliability of the principal diagnosis fell from 73.5% for cases with a single diagnosis to 54.7% for cases with multiple diagnoses (14); approximately 90% of our cases had multiple diagnoses. Our data show a reviewer DRG-reassignment rate of 33%. To our knowledge, no prior study has looked at reliability of DRG assignments.

Selection between justifiable multiple DRGs was based on the goal of maximization of reimbursement. This yielded a potentially "profitable" change in almost 25% of cases, supporting the concept that the manner in which a physician documents the chart affects DRG categorizing and reimbursement.

The reasons for physician and reviewer differences of primary diagnosis and DRG assignment are (a) the physician inadequately documents the face sheet; (b) the reviewer finds the physician assignment of the primary diagnosis inappro-

TABLE 6

DRG-Based Reimbursement: Varying Totals

	Total Reimbursement	Addition to Abstractor Total $(%)	
Abstractor-assigned DRG	$136,337	—	(—)
Reviewer-assigned DRG	$142,385	$6,012	(+4.4)
Reviewer-maximized DRG	$148,507	$12,170	(+8.9)

TABLE 7

DRG-Relevant Additions to Face Sheet

Abstractor DRG-relevant additions	25/43 (58%)
Change in substantial complication-comorbidity	
After abstractor additions	7/43 (16%)
After reviewer additions	3/43 (7%)

priate to the information in the chart; (c) multiple justifiable diagnoses are possible; and (d) the reviewer commits a clerical error or an error of judgment. In addition, when DRGs are maximized for reimbursement, with multiple justifiable diagnoses and DRGs possible, the physician makes a diagnosis assignment based on unspecified criteria, while the reviewer may assign DRGs based on the highest reimbursement potential of justifiable diagnoses. In the recording scheme we used to analyze the basis for discrepancies in either the diagnosis or the DRG, reasons (a) and (b) are considered "physician error," (c) is "disease overlap of diagnosis/DRG category," and (d) is "abstractor error."

When we examined the reasons for reviewers changing the primary diagnoses, we found equal numbers of physician errors and disease overlap (Table 2). The cases with disease overlap reflect the ambiguity of criteria for diagnostic designation and the difficulty of selecting a primary diagnosis in a patient with multiple medical problems. The disease overlap of a patient with multiple disorders, including COPD, under the care of a large medical team, could obscure the documentation of the condition which was most important for the admission. Diagnosis overlap was the reason for change of diagnosis in 4 of the 5 cases of congestive heart failure (the fifth case was physician error, failing to note the diagnosis at all) and 3 of 4 cases of pneumonia (the fourth case was an abstractor-generated miscoding). This supports the premise that there are common patterns of disease-overlap errors.

A number of physician errors caused the reviewer change of primary diagnoses. Two of 43 face sheets (5%) had no physician comments at all. One patient with chronic lung disease was found to have a subendocardial infarction as the cause of pulmonary edema; there was no documentation of an infarction anywhere on the face sheet, though it was clearly documented in the physician notes. Another physician listed five diagnoses as the primary diagnosis, including controlled diabetes mellitus and glaucoma, neither of which affected the hospital course. In many cases, the physician listed an underlying chronic disease as the primary diagnosis, although an isolated acute disease prompted the hospital stay and was more appropriate as the primary diagnosis.

Fiscal Analysis of DRGs. Our findings support the supposition that physician documentation of diagnoses can have important effects on DRG-based hospital reimbursement. The 4.4% increase in potential reimbursement (Table 6) was based on 14 medical-reviewer changes in DRG assignment. Among the reassigned cases, some of the new diagnoses were of greater dollar value and some of lesser as compared with COPD. For those 14 cases with more than one justifiable DRG, when choice of DRG was made on the basis of the higher dollar value, 4 of 14 were reclassified as COPD, and 10 of 14 were reassigned to other DRGs with a dollar value higher than that of COPD. In these cases, there was potential of almost 9% increased hospital reimbursement above the abstractor-assigned DRG reimbursement.

The lack of reliable discharge data on the face sheet when DRG-based reimbursement is dependent on face-sheet information could create problems in health care planning. Simborg has commented on the inaccuracies that occur in the listing of diagnoses as primary and secondary, and, further, how hospitals could attempt to maximize profits by listing the most financially beneficial of a patient's diagnoses as the primary one regardless of its medical rationale (15). As an example, by reversing the sequence of primary and secondary diagnoses of 159 patients undergoing a major urological surgical procedure at his institution, he could alter the reimbursement potential of these patients by $800,000. He identifies "DRG creep" as the practice of utilizing computer programs or other means to determine the sequencing of diagnoses which will yield the highest possible reimbursement and questions its ethics. We have shown that, without unethical manipulation of medical data, the designation of primary diagnoses can be arbitrary. In many cases this can have important monetary ramifications.

We have made many simplifications in our analysis of DRG-based reimbursement. The dollar values per DRG used to calculate total reimbursement for our study are not figures derived for our hospital and are not corrected for our urban status, teaching status, wage index, historical Medicare costs, and other specific reimbursement criteria used in prospective payment plans. We did not limit our patient sample to Medicare patients, nor did we try to determine if patients studied had lengths of stay beyond those allowed for their diagnosis, making them outliers and outside the boundaries of DRG-based reimbursement. We believe, however, that assignment of unadorned dollar values per patient DRG is a rough but reasonable means to compute reimbursement figures.

DRG-Relevant Additions to Face Sheet. We have shown that a significant number of DRG-related diagnoses are missing from physician-compiled face sheets. In our study, physicians failed to fill out face sheets in approximately 5% of reviewed charts; this is less than the 14% average at our hospital (16). Almost 60% of charts reviewed had medical abstractor additions that could affect DRG assignment. Seven patients had a change in comorbidity-complication status, one of the major criteria for designation of DRGs. Furthermore, we identified three patients whose complication-comorbidity status changed on the basis of information found in the chart; this data had not been brought to the face sheet by either the physician or the medical abstractor.

While these findings support the premise that physicians incompletely report information that can affect DRGs and reimbursement, the findings do not definitively address the question of the adequacy of documentation. It could be argued that the data substantiate the role of medical abstractors and that physicians' documentation is adequate as long as the end result is a complete medical record and face sheet. However, if accurate assignment of DRGs requires clear designation of primary and secondary diagnoses and procedures on the face sheet, then, in these terms, physicians' face sheets are inadequate.

Design Limitations. One disadvantage of using COPD as the tracer diagnosis was the lack of complication-comorbidity criteria governing COPD as a DRG in the flow scheme (Fig. 2). For this reason, changes in complication-comorbidity status of ten patients did not alter the DRGs. Another limitation of using a single tracer diagnosis is the inability to easily generalize to other diagnoses. Three Institute of Medicine studies have documented a variation in reliability of different diagnoses. For example, rhinoplasty is a more reliable diagnosis than pancreatitis (9, 10, 14). We suspect a similar variation in interdiagnosis reliability with DRGs.

Another weakness of our study design was the time of entrance into the flow of chart processing (Fig. 1); we did not look at all charts on which physicians listed COPD as the primary diagnosis, but only those charts on which the medical abstractor coded the appropriate ICD-9 code number. In this way, we failed to identify false negatives—charts with the physician's primary diagnosis as COPD, but reabstracted or clerically coded to another ICD-9 number. We could not estimate the extent of such errors, but believe they may be common. Fourteen of the 41 charts we reviewed (34%) with face sheets completed by physicians had more than one diagnosis listed as the primary diagnosis; only COPD was ICD-9 coded as the primary. The second, uncoded "primary" diagnosis would be a false negative if a separate study used that diagnosis as the tracer. Another type of false negative exists when the physician misdocuments a diagnosis which is not corrected by the abstractor. An example is a patient who has COPD with bronchospasm who is given the diagnosis of pleural effusion although none exists, and whose chart is coded for the effusion. To identify all false negatives, it would be necessary to review all hospital charts for a specified time period.

Another unresolved issue in study design is the question of reviewer bias in determining what is acceptable as a different medically justifiable diagnosis. In medical-records abstracting as well as in the process of differential diagnosis a huge body of knowledge is called into use, subject to the ambiguity of criteria of definition and organization. We attempted to minimize bias in each instance of uncertainty by reviewer consensus, but in a more carefully controlled study one would review the chart without knowledge of face sheet material or ICD-9 number.

Finally, we did not evaluate the reliability of the chart for its adequacy either as a tool to make valid diagnoses or as a reflection of what the physician truly believes the diagnosis to be.

Summary

The introduction of a nationwide prospective payment system based on DRGs mandates changes in the availability of medical funds. Since physicians' documentation of medical records can affect DRG assignment, and consequently reimbursement, physicians must be made aware of the problems in reporting data and

the need to complete face sheets adequately. This process may require increased emphasis in medical schools on teaching diagnosis classification schemes and aspects of probabilities as they pertain to disease. In some cases it may be difficult to use medical criteria to designate one diagnosis as more "primary" than others. In the past, arbitrary assignment of the patient with multiple medical problems into a particular primary diagnosis category had little if any consequence; under the new prospective payment scheme, diagnoses will be directly translatable into dollars, and these decisions will have significant financial impact.

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Anthracycline Antibiotics as Cellular Disruptors: Insights into Anthracycline-Induced Cardiomyopathy

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ABSTRACT

The biochemical phenomena that constitute the primary anthracycline insult to the heart are unknown. We examined the loss of cardiac contractile function through the interactions between this antineoplastic and selected purified protein constituents in vitro and in vivo. Our in vitro studies revealed that Adriamycin interacted with actin, inducing atypical actin polymerization in the absence of K^+ or Mg^{+2}. Our in vivo studies revealed that exposure of heart cells to Adriamycin radically altered protein synthesis. Among the cytoskeletal constituents, actin synthesis was least affected by Adriamycin, as compared with its effects on other sarcomeric proteins.

The observed direct effects of Adriamycin on purified myofibrillar proteins together with studies of heart cells in vivo support the view that Adriamycin induces subcellular derangement of the contractile apparatus. Since other mechanisms are involved in Adriamycin-induced cardiac myocyte injury, they have been included in this review.

Although the action of ADR on neoplastic and cardiac cells may follow similar biochemical mechanisms, the damaging effects of the drug apparently differs according to specific properties of the cell type involved. Whereas ADR inhibition of DNA replication would severely hinder the active division of neoplastic cells, the cardiotoxic action of the drug may be more closely related to DNA-directed activities, such as protein synthesis, which maintain the integrity of intact cells. Similarly, the direct effects of ADR on myofibrillar proteins could play a significant role in deranging myofibrils, ultimately destroying the cardiac cell. The experimental utility of ADR in studying of congestive cardiomyopathy is being recognized, and we postulate that this drug will likely become a probe for cell disruption.

Doxorubicin hydrochloride (Adriamycin, ADR), an anthracycline antibiotic, is a well-known chemotherapeutic agent used in the treatment of a variety of malignancies. A major iatrogenic effect of this drug is dose-related severe irreversible cardiotoxicity. Clinically, this cardiotoxicity is manifested by evidence of congestive heart failure, including poor pump function, pulmonary congestion and edema, peripheral edema, and death. Fortunately, if the therapeutic regimen is carefully monitored to maintain the cumulative dose below 500 mg/m^2, patients less frequently develop these cardiovascular complications (1).

ADR-induced cardiomyopathy bears a resemblance to congestive cardiomyopathy from other causes (2) and provides a valuable experimental model for the controlled study of this disease. ADR can be administered in vivo to simulate congestive cardiomyopathy in animal species, including dog, rat, mouse, and rabbit (3–6). Based on morphologic comparisons, the dog and rabbit are still the most useful animal models for the study of ADR heart-muscle disease.

Using our system of primary cultured cardiac myocytes (CCM) coupled with biochemical

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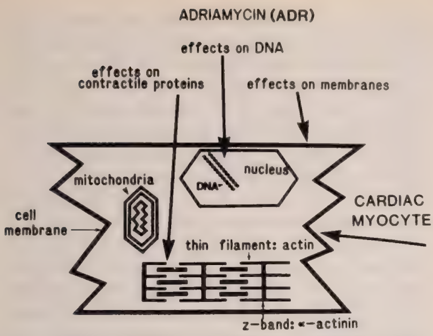

FIG. 1. Subcellular Effects of Adriamycin (ADR) on the Heart Cell: This schematic diagram of a heart cell shows the postulated disruptive effects of ADR on cardiac cell function.

studies on purified contractile proteins, the examination of the pathological and biochemical effects of ADR on cells was facilitated (7–11). CCM offered the advantages of being similar in vivo to cardiac tissue and cells (CCM have abundant mitochondria and well-formed sarcomeres); and use of CCM permitted the cells to be examined without systemic input from the organism.

ADR served well as a biochemical probe for tissue-culture studies. First, it is soluble in both aqueous and some organic media. Second, it is rapidly taken up by the cells. Third, it has 2 pKa's and a quinone structure, with indicator properties. Fourth, it binds strongly to DNA, and fifth, it is fluorescent. These properties enable ADR-CCM interaction to be monitored by a variety of chemical and physical techniques as well as direct visual observation of the cells by fluorescent microscopy.

The importance of studying ADR effects on the heart experimentally is twofold. Clinically, its chemotherapeutic utility underlies the need to determine the molecular basis of its cardiotoxicity; in time, findings may lead to the development of a related, effective antineoplastic with reduced cardiotoxicity. Experimentally, studies of ADR may provide new insight for the understanding of congestive cardiomyopathy.

In our recent work on ADR, we have grouped its effects according to the nature of the cellular damage, and we have reviewed experimental evidence for ADR's interactions with nuclear DNA, its injury of the cardiac myocyte membrane, and its effects on myofibrillar proteins (Fig. 1).

ADR and Its Effects

Adriamycin was first isolated as a product of *Streptomyces peucetius* var. *caesius* in 1963 (12). Congeners of ADR have also proven to be useful antineoplastics, most prominently daunomycin (DM), which differs from ADR by a single hydroxyl substitution at carbon 14. ADR contains an amino sugar, daunosamine, in a glycosidic linkage with adriamycinone, forming a naphthacene-quinone ring. The latter structure is responsible for the brilliant red color of this drug.

Three major mechanisms play roles in the ability of ADR to kill tumor cells. The mechanisms may be interrelated, but each takes part in disturbing the homeostasis of neoplastic cells. Intercalation with DNA is well-documented for all anthracycline antineoplastics, particularly ADR. ADR inserts itself into double-stranded DNA so that the quinone moiety is stacked between base pairs and parallel with them. The sugar portion of the ADR molecule can thus bind to the phosphate backbone of DNA. These chemical interactions are considered responsible for the high binding affinity of ADR for DNA, a binding that produces deleterious effects on the cell: DNA polymerization is thwarted; inhibition of DNA repair enzymes has been reported (13, 14); and ADR has been shown to interrupt transcription of DNA to RNA and consequently to inhibit protein synthesis of tumor cells in tissue culture (13, 15).

The cytotoxic effects of ADR may also result from the binding of the drug to cellular membranes. This interaction may account for alterations in membrane Na^+/K^+ adenosine triphosphatase (ATPase) (16, 17), mitochrondia metabolic output, and membrane activity (18). Cardiolipin, a membrane lipid, abundant in both tumor and heart cells, avidly binds ADR (19–21). Studies have shown that ADR can alter a variety of cell surface receptors, including concanavalin A (22), and calcium channels (23, 24).

Another action of ADR on the cell may involve microsomal free radical production. An enzymatic alteration of the ADR moiety can occur, resulting in a semiquinone free radical which converts molecular oxygen to a superoxide form (25–31). Other enzyme systems, too, can potentially reduce ADR to the semiquinone, yielding oxygen radicals. Evidence exists to support the belief that this mechanism is operative in both heart and tumor cells (32).

Our hypothesis concerning ADR-induced myocyte damage was based on the observation of disruption of the sarcomere (particularly the Z-disc and thin filaments) in ADR heart muscle disease. We explored the interaction of ADR with the purified protein constituents of ultrastructural organelles in the heart cell and correlated our biochemical findings with observed changes.

Effects of ADR on DNA, RNA, and Protein Synthesis. Nuclear DNA is a major site of the action of antineoplastic anthracyclines in vivo, primarily because of the binding of anthracyclines to DNA (33–36). Studies of drug uptake and distribution in cultured cells demonstrated by fluorescent microscopy that both ADR and DM (daunomycin) are rapidly taken up from the culture medium and localized in the nucleus (37–39). Experiments with cell homogenates confirmed that nuclear binding of anthracyclines can account for as much as 70% of total intracellular binding (40). Our results showed that 20%–30% of the drug bound to the nuclear fraction of heart cells using ^{14}C-ADR and ^{14}C-DM on cultured cardiac myocytes.

Adriamycin forms intercalation complexes in the nucleus through noncovalent binding with double-stranded DNA (33). Evidence for this interaction came from drug-induced changes in the spectroscopic properties of DNA, its sedimentation rate, viscosity, and denaturation profile (34, 41). A model for the formation of the DNA-anthracycline complex proposes that the planar aglycone moiety inserts itself between the hydrophobic faces of adjacent base pairs, thus allowing the daunosamine-sugar moiety to bind ionically to the sugar-phosphate portion of the DNA (33). Independent studies demonstrated that ADR and DM require guanine-cytosine base sequences at binding sites and exhibit the highest affinity for purine-pyrimidine sequences (42, 43). The great affinity of ADR for DNA ($Ka = 6 \times 10^{-5}M^{-1}$) facilitates the accumulation of the anthracycline in the nuclear compartment. Furthermore, ADR-Fe^{+3} may form a stable complex with DNA that can break DNA strands in the presence of reducing substances such as glutathione (44).

Studies of radio-labeled nucleotide incorporation suggested that the formation of the DNA-anthracycline complex can result in inhibition of DNA replication and repair (13). This action by ADR may ultimately impair RNA synthesis, reduce the cellular content of ribosomal RNA and messenger RNA, and subsequently inhibit protein synthesis (45). Proposed pathways for the inhibition include prevention of DNA strand separation by ADR (35) and hindrance of polymerase binding due to DNA structure distortion.

The inhibitory effects of ADR on DNA replication differ significantly from its effects on DNA repair. In ultraviolet-damaged cardiac cells from neonatal rats, cells treated with ADR underwent repair by unscheduled DNA synthesis at low doses of the drug but not at higher doses. Differences between repair and replication inhibition became evident at ADR doses (10^{-6}M) which reduced DNA replication by as much as 75% without inhibiting repair. The effect of ADR may be localized around the intercalation site, thus interfering with the integrity of the polymerases without affecting repair enzymes (14).

Additionally, ADR can disrupt the structure of DNA through mutagenic changes, such as strand breakage (46–48). This damage may result from the interaction between DNA and the semiquinone free radical intermediate of the anthracyclines (47). The ability of anthracyclines to block DNA replication may account for the effective inhibition of mitosis in cancer cells. The mechanism(s) of anthracycline-induced cardiomyopathy, however, may be less related to its direct effects on DNA since adult cardiac myocytes are characterized by mitotic quiescence (6).

The role of RNA in protein synthesis may be important in the cardiotoxic action of anthracyclines. In vivo studies of ADR-treated mice (5) demonstrated an inhibitory effect of the drug on RNA synthesis following both long-term and acute treatment. Both the duration and extent of inhibition were dose-dependent. The observation that ADR inhibits activity of RNA polymerase II of chicken myoblastosis cells in vitro suggests that the ADR-induced depression of RNA synthesis may be enzymatically related (49). Messenger RNA and ribosomal RNA were both shown to be inhibited by ADR. In myocardial cells, ADR reduces a greater percent of messenger RNA than of total and microsomal RNA (45, 50, 51). This latter observation suggests that ADR acts predominantly on the nucleus, rather than on the nucleolus.

In vitro studies of protein regulation in cardiac myocytes showed decreased messenger RNA content in ADR-treated cells, with subsequent reductions in protein synthesis. Given the known half-lives of cardiac contractile proteins (45, 50, 51), an inhibition of protein synthesis could produce a gradual loss of cardiac structure and function. A protracted course of deteriorating cellular function is consistent with the clinical presentation of ADR-induced cardiomyopathy.

Adriamycin-Membrane Interactions. Adriamycin binds to cell membranes, yet the importance of membrane interactions to the cytotoxic action of this class of drugs has not been elucidated. Experimental findings show that both immobilized ADR (52) and AD-32, a congener of ADR (39), exhibit effective antineoplastic activity without undergoing cellular internalization.

Other reported effects of ADR at or below concentrations affecting DNA function have included changes in membrane morphology (53), ion transport (16, 17, 23, 24, 54, 55), lipid organization (21), membrane fluidity (56), and lectin-induced cell agglutinization (22). Anthracycline-induced oxygen free-radical formation has also been studied as a potential cause of membrane damage (25–30, 32).

Although the specific membrane receptor sites for ADR are not known, the anthracycline has been reported to bind to spectrin, a cytoskeletal protein of the erythrocyte membrane (53), and to membranes containing anionic phospholipids, including cardiolipin (20, 21, 57). In model membrane systems, the presence of cardiolipin increased ADR-membrane binding. This effect may result from electrostatic interactions between the positively charged drug and negatively charged phospholipids (e.g., cardiolipin), as well as from cardiolipin-induced alterations in the organization of the lipid bilayer (57, 58). The presence of cardiolipin may account for the drug selectivity for cardiac and neoplastic cells—both these cell types are characteristically rich in cardiolipin. The abundance of cardiolipin in cardiac myocytes is due to the great number of mitochondria in these cells (58).

Free-radical-mediated mechanisms are invoked to explain the cytotoxic and cardiotoxic action of ADR. As in other quinone-containing antineoplastic drugs, the quinone moiety of ADR can undergo reduction to the hydroquinone, through the formation of a semiquinone free radical intermediate. This reaction may be mediated by cytochrome P-450 reductase or other flavin-dependent oxidation systems (25–27). Subsequent autooxidation of the semiquinone may occur, generating superoxide radicals, which can decompose to yield hydroxyl radicals and hydrogen peroxide (29). The semiquinone and superoxide radicals can interfere with cellular oxidation-reduction reactions; they also initiate electron-transfer chain reactions which induce potential damage to cell membranes by converting unsaturated fatty acids to lipid peroxides (28).

The conversion of ADR to the free radical form was demonstrated in isolated cardiac submitochondrial particles and in microsomal preparations from the heart, liver, lung, and spleen of rats and mice (29, 59). Tissue damage related to lipid peroxidation in vivo was detected in ADR-treated cells in culture (22) and in the hearts of ADR-treated mice (5). The daunosamine moiety of ADR may influence the ability of the quinone of ADR to stimulate lipid peroxidation by stabilizing the interaction between the anthracycline and the flavin mononucleotide of cytochrome P-450 reductase (31, 60). ADR may also produce a dose-dependent stimulation of endogenous NADH-dependent lipid peroxidation (31, 61).

An alternative mechanism of peroxidation may involve the complexing of divalent and trivalent cations, particularly iron, to ADR. Oxidative destruction of human erythrocyte ghosts by ADR-iron complexes has been reported (44). The complex, with a composition of two moles ADR per mole Fe^{+3}, binds to membranes and initiates membrane destruction by generating high local concentrations of reactive oxygen species at the membrane surface. The existence and behavior of this complex under physiologic conditions may explain the observed increase of lipid peroxidation in the presence of Fe^{+3} and suggest a mechanism for ADR-induced lipid peroxidation in the heart. The chelating agents ICRF-159 and ICRF-187 have been shown to reduce the toxicity of ADR on the heart (62, 63). This finding further supports the hypothesis that the availability of iron to ADR can enhance its cardiotoxic effects (44, 64).

Lipid peroxidation may be more severe in the heart than in other tissues. As compared with the liver, the heart (45) contains low levels of extractable glutathione peroxidase, catalase, and superoxide dismustase (28, 32, 63)—all enzymes that are active in free-radical detoxification. Moreover, ADR is reported to reduce cardiac glutathione peroxidase pools, thereby further impairing the limited ability of cardiac tissue to defend against free-radical damage (63, 64).

The properties of α-tocopherol (vitamin E) and other antioxidants and free-radical scavengers have been investigated as defenses against oxidative destruction (32, 65). In vivo studies in mice and rats demonstrate that pretreatment with exogenous α-tocopherol reduced ADR toxicity (32, 65). Although the ability of vitamin E to inhibit lipid peroxidation is known, ADR toxicity in animals pretreated with α-tocopherol is not substantiated.

Other membrane alterations involved in the cardiotoxic action of ADR include changes in membrane permeability and ion transport. ADR-induced changes in Ca^{+2} concentration and availability may bear particular relevance to the cardiotoxic action of the drug. The dependence of heart muscle on extracellular Ca^{+2} concentration is widely recognized (66). Removal of this ion from the perfusion medium produces an abrupt fall in cardiac contractile force (66). Furthermore, significant accumulation of intracellular Ca^{+2} is known to damage mitochondrial metabolism and to alter excitation-contraction coupling (18, 67). Calcium overload is thought to break down myocardial adenosinetriphosphate (ATP) and creatine phosphate, thus reducing the substrates available to high-energy phosphates in the cell (68).

Adriamycin may produce decreased myocardial contractility by inducing a shift of Ca^{+2} from rapidly to slowly exchanging pools. The rapidly exchanging Ca^{+2} fraction, bound to abundant low-affinity sites on the membrane, modulates contractility by supplying Ca^{+2} to the contractile proteins, while the less abundant slow-exchanging fraction helps maintain the integrity of the membrane. The correlation between ADR-induced changes in Ca^{+2} exchange and impaired contractility was supported by studies of spontaneously beating isolated guinea pig atria. In the presence of ADR, these demonstrated decreases in both contractile force and uptake of $^{45}Ca^{+2}$ from the medium.

ADR Direct Interaction with Contractile Proteins. The interaction of ADR with cardiac contractile proteins has been studied in vitro and in vivo in our laboratories (7–11) and in those of others (45, 50, 51, 69). Our in vitro studies using purified cardiac contractile proteins were undertaken to investigate the biochemical phenomena responsible for the morphologic alterations observed. Ultrastructural changes in the sarcomere include splaying and disruption of the Z-disc and thin filaments. Based on these observations, we chose to purify α-actinin and actin, the primary protein components of these sarcomeric structures, and to examine their interactions with the drug.

Our initial studies demonstrated binding of ADR to α-actinin. Studies on actin revealed that ADR binds to G-actin in a molar ratio of 2–4:1. Preparations of G-actin incubated with ADR (10^{-5} to 10^{-6}M) in the absence of K^+ were observed by negative staining electron microscopy. These revealed the formation of fascicular filaments, 12–16 nm in thickness, which differed from the 6–7 nm F-actin filaments polymerized by K^+. The ADR-induced actin filaments demonstrated an ability to interact with rabbit back-muscle myosin and to allow for ATP hydrolysis by the hybrid actomyosin complex. This ATPase activity was as high or higher than the activity observed in the K^+-polymerized-actin controls incubated with the same myosin. This result differed from previously reported findings of decreased ATPase activity in rabbit back-muscle myosin (69). Correlative viscometric studies of ADR-actin interactions revealed that, despite the formation of such unusual filaments, actin incubated for 30 min with 10^{-6} to 10^{-3}M ADR behaved biophysically like G-actin. Sequential time studies of ADR-induced polymerization are currently under way.

ADR-actin fascicles were examined further by negative staining electron microscopy and showed high affinity for myosin and heavy meromyosin (HMM) decoration. When G-actin and HMM were incubated with ADR in the absence of K^+, arrowhead-decorated actin filaments were formed preferentially, compared with ADR-actin fascicles. ADR-induced actin fascicles were studied biochemically to determine the polymerization state. By DNA-ase I inhibition the fascicles were assayed for oligomeric and monomeric actin. Pancreatic DNA-ase I, a deoxyribonucleic acid hydrolase, binds to monomeric and oligomeric actin with high affinity and is inhibited by actin binding. DNA-ase I inhibition assays were performed on actin incubated with ADR (10^{-6} to 10^{-5}M) and on purified G-actin in the absence of ADR. ADR (10^{-6}M) reversed DNA-ase I inhibition by G-actin after one hour of incubation, and this enzyme activity remained stable for up to three hours of incubation. (Lewis et al, unpublished data).

The data imply that an unusual group of phenomena occurs when ADR interacts with actin in vitro: (a) actin is able to form polymers in the absence of K^+; (b) the polymer formed in the presence of ADR appears to function partially like F-actin (based on ATP-ase assays), yet biophysically the filament has some resemblance to G-actin; and (c) DNA-ase activity could not be inhibited by actin treated with ADR, implying that the ADR-treated actin is unable to bind to DNA-ase I. This last can be explained by noting that the formation of filaments (or polymers) of G-actin leaves fewer actin monomers available for DNA-ase I inhibition.

The Binding Site for Actin

Experimental evidence implicates the free amino group of the daunosamine sugar of ADR as the binding site for actin. Affinity chromatography, using G-actin covalently linked to a Sepharose matrix, showed that ADR bound at low ionic strength. The anthracycline bound to the matrix could be eluted only with the addition of a high salt to the buffer. Control affinity columns, using IgG or fibrinogen ligated to the matrix, showed no retention of ADR, implying some specificity of the binding of ADR to actin. In reciprocal experiments, ADR was ligated to the gel matrix through its primary amino group. Purified G-actin and α-actinin were not retained by the ADR affinity column.

To further test the postulate that the free amino group of ADR is the binding site of actin, we have recently dimerized ADR, using cross-linking reagents which react specifically with primary amino groups. The solitary primary amino group of ADR reacted with dimethyl suberimidate (DMS) to form a mirror-image dimer composed of Adriamycin bound to an identical sister molecule through amide linkages with DMS. This compound (trivially called "diADR"), which has no free amino group, may be separated from ADR by thin-layer chromatography or by CN-Br Sepharose 4B column chromatography. We have achieved an analytical purification of diADR by taking advantage of ADR's affinity for actin. Using CN-Br-Sepharose 4B conjugated with actin, we took the ADR-DMS mixture and passed it through the actin affinity column. Two peaks eluted on affinity chromatography, the first with the running buffer, the second with the addition of 0.4–0.6 MKCl. The first peak comigrated with diADR on TLC. The latter peak co-migrated with ADR. This provided further evidence that the free amino group of ADR's daunosamine is the site for actin binding: The diADR, unlike ADR, has no free amino group and thus eluted unretarded from the actin affinity column. Further work with diADR is actively under way in our laboratories.

Effects of ADR and DM on Cultured Cardiac Myocytes

The uptake and binding of ADR and DM by cultured cardiac myocytes (CCM) in vivo has been explored using ADR and DM, tagged with carbon 14, and discontinuous sucrose gradient fractionations of CCM cell homogenate. The results demonstrated that both ADR and DM were concentrated in the light-buoyant-density fractions (5%–15% sucrose) as well as in the nuclear pellet. The incorporation rate remained unchanged in 1–8 hours of exposure to either drug. Addition of ATP (10^{-4}M) to the medium inhibited the uptake of ^{14}C-ADR but not ^{14}C-DM in the light-buoyant-density fractions of the cellular homogenates.

In our in vivo studies, the affinity of ^{14}C-ADR and ^{14}C-DM for cultured embryonic heart cells was determined by measuring their uptake, their compartmentalization into subcellular fractions, and the effect of this on the synthesis of cytoplasmic and cytoskeletal proteins. We found that both drugs, at μM concentrations, were located in a light-buoyant-density fraction containing no lysosomes. In addition, the nuclear ^{14}C drug-content accounted for 20%–25% of the radioactivity recovered. Binding of ADR was saturable within 90 min of drug exposure, and the uptake of ^{14}C-ADR was inhibited 50% by ATP and by a Ca^{+2}-channel blocker, Verapamil. Uptake of ^{14}C-DM was not influenced by these compounds. Cytosolic and cytoskeletal protein synthesis, measured by ^{35}S-methionine incorporation into proteins, was blocked 70% overall in each fraction after 6 hours incubation with 2 μM ADR. Sodium-dodecyl-sulfate polyacrylamide gel electrophoresis followed by autoradiography and quantitative densitometry revealed that actin synthesis was the least affected of the major proteins. Cardiac myocytes incubated for short periods of time with 2 μM ADR revealed subtle cytoplasmic changes in their organelles, with the appearance of clear zones of cytoplasm containing short unorganized microfilaments.

Effects on Contractile Function

Studies using perfused hearts (68) demonstrated a dual effect of ADR on Ca^{+2}-modulated contractile function: a positive inotropic effect of ADR was observed at low concentrations of the drug, but this was reversed at higher concentrations. A proposed mechanism for ADR-induced heart-muscle disease is based on ionic alterations and homeostatic readjustments by the cell. According to this hypothesis, an increased Ca^{+2} influx produces elevated levels of intracellular Ca^{+2}, which increase contractility. This contractile state strains the available energy supply, thus reducing the availability of ATP for cellular function and maintenance. Ultimately, the deteriorated cell exhibits diminished contractile ability. Concurrently, increased Ca^{+2} uptake by the mitochondria causes structural and functional damage to this organelle, resulting in reduced ATP production.

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Complementary Effect of Cholecystokinin-Octapeptide and Soy Flour Treatment in Chronic Pancreatitis

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Abstract

The effects of intranasal cholecystokinin-octapeptide (CCK-OP) treatment and of a soy flour diet were investigated in 20 patients with chronic pancreatitis. Two drops of a 1 mg ml CCK-OP solution, given three times daily, and 30 gm of raw soy flour, also given three times daily, were administered for one month, in random order, with an interval of about 13 months between the treatments. The enzyme secretory capacity of the pancreas, as measured by the Lundh test, increased by 108% after the soy flour treatment and by 54% after the CCK-OP treatment. The results of the two courses were cumulative in the case of lipase and amylase; in trypsin secretion, some relapse occurred between the treatments. The secretin-pancreozymin test showed an increase similar to that found by the Lundh test. The water and bicarbonate secretion did not change. The two courses supplemented each other; patients who did not respond to one of the treatments did improve after the other.

The trophic effect of cholecystokinin octapeptide (CCK-OP) and that of raw soy flour diet are well established in rats (1–3). In previous studies we have demonstrated that in patients with chronic pancreatitis either the administration of intranasal CCK-OP for three weeks (4, 5) or soy-flour treatment during one month (6, 7) resulted in about a twofold increase of pancreatic secretion. The results were attributed to the trophic effect of exogenous and endogenous CCK on the human pancreas.

In some patients, however, treatment by one agent only was insufficient; later pancreatic secretions tended to return to pretreatment levels. In these cases, a subsequent course of the other treatment was also administered after about one year. The results of the two courses were compared and the cumulative effect of the two treatments was investigated in this study. Some preliminary data has already been presented (7).

Material and Methods

The study was performed with 20 patients with chronic pancreatitis (6 women and 14 men, mean age 42.6 ± 2.78 years). Some of them had participated in one of our earlier studies of CCK-OP (5) or soy flour (7). Eleven patients formerly had consumed more than 50 gm/day of alcohol, but they stopped drinking at least nine months before the first treatment. Two patients had undergone biliary-tract operations years before the study, but thorough radiological examinations revealed no retained stones or microlithiasis. In 7 patients, no definite etiological factor was detected.

Diagnostic Criteria. In our previous studies (5, 7), screening tests were performed, supplemented by the secretin-pancreozymin test or the Lundh test, repeated after a six-month period. In 6 patients surgery, and in 5 patients endoscopic wirsungography, verified the morphological characteristics of chronic pancreatitis.

Patients were classified as having mild (6 patients), moderate (7 patients), or severe (7 patients) chronic pancreatitis according to their exocrine pancreatic function as measured by the se-

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cretin-pancreozymin or the Lundh test. Two patients with severe chronic pancreatitis had manifest diabetes and steatorrhea. In 1 among the moderate cases and in 2 of the mild cases impaired glucose tolerance was demonstrated.

Technical details concerning the secretin-pancreozymin and Lundh tests have been reported previously (5, 7).

Calculation. Mean enzyme activities and cumulative enzyme outputs were calculated for trypsin, lipase, and amylase measured in 10-min samples of duodenal juice stimulated by synthetic secretin plus CCK-OP and the Lundh test meal. These values as well as volume output and maximum bicarbonate concentration were expressed as percent changes from values found at the beginning of the CCK-OP or soy flour treatment taken as 100%. Overall mean relative values of enzymes (the sum of percent changes divided by 3) were also calculated to represent changes in the total capacity of enzyme secretion (5, 7). The cumulative effects of the two treatments were expressed as percent changes after the second treatment from pretreatment values (100%).

The results were statistically evaluated with Student's *t*-test for paired values.

Treatments. CCK-OP was administered in the form of intranasal drops from a solution containing methyl-cellulose with a CCK-OP concentration of 1 mg/ml. Two drops three times daily before meals were given for 3–4 weeks (4, 5).

For one month, 3 gm of raw soy flour was administered three times daily 15 min before each meal, in 250 ml of water (6, 7). For 10 patients the CCK-OP treatment was performed as the first course. For the other 10 patients the soy flour treatment was given first. Intervals between the two treatments were 3–45 months (mean, 13.5 ± 2.44 months).

In every case a Lundh test, followed 3 months later by a secretin-pancreozymin test, or a Lundh test before the beginning of the treatments, had shown that the disease was stable. Two days after the last administration of the CCK-OP or the soy flour, a third secretin-pancreozymin or Lundh test was performed to measure changes in the exocrine function of the pancreas. For 18 of the 20 patients treated with CCK-OP and for 19 patients who had the soy flour treatment, a final Lundh test was given after a 3-month period to check the long-lasting effects of the treatments.

For each patient, the second course of treatment involved the same examinations as the first, so all the patients were examined at least six to seven times during the study. At these examinations detailed inquiries revealed the course of symptoms during and after the treatments, thus enabling the comparison of one treatment to the other.

Results

Only those patients were selected for the study who did not heal spontaneously during the pretreatment period. Moreover Lundh tests at the beginning of treatment showed a decrease of 6%–15% (not significant) from results three months prior to beginning treatment (Fig. 1).

All patients were checked with Lundh tests. The overall output of enzymes improved after CCK-OP by 54% and after soy flour treatments by 108% (Fig. 1). The overall enzyme activity increased at similar rates.

Enzyme output as measured by the Lundh test did not increase in 6 patients after CCK-OP treatment and in 2 patients after soy flour treatment. However, in the two patients who did not respond to soy flour, CCK-OP treatment succeeded in increasing significantly their enzyme secretion. In the two soy nonresponders, the effect of CCK-OP was more pronounced than the effect of soy flour.

After the soy flour treatment, the increases in trypsin and amylase secretion were somewhat more pronounced than the lipase increases. The CCK-OP treatment augmented production of the three enzymes almost equally, but the increases in trypsin and amylase output did not attain that seen after the soy flour treatment (Fig. 2). Secretin-pancreozymin tests were performed before and after treatment for 12 of those patients treated with CCK-OP and 13 treated with soy flour. The overall changes shown by secretin-pancreozymin test were essentially the same in these patients as those shown by the Lundh test (Fig. 3). The water and bicarbonate secretion did not change significantly after the treatments (Fig. 3).

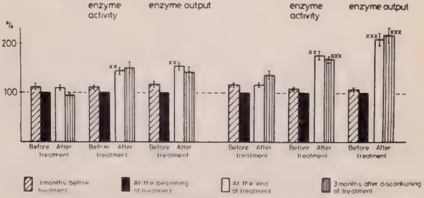

FIG. 1. Changes in Lundh test results before and after CCK-OP and soy flour treatments. Values are mean ± SE of 20 patients. Significant differences from 100% are indicated as x ($p < .05$); xx ($p < .01$); xxx ($p < .001$).

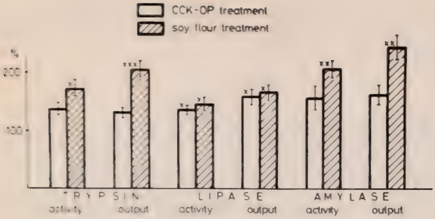

FIG. 2. Increases in enzyme values of Lundh test after CCK-OP and soy flour treatments. Values are mean ± SE of 20 patients. Significant differences from pretreatment results (100%) are indicated as in Fig. 1.

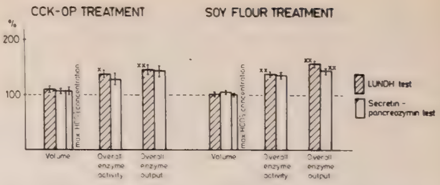

FIG. 3. Comparison of the increase in Lundh test and secretin-pancreozymin test results after CCK-OP and soy flour treatments in the same patients. Values are mean ± SE of 12 patients in our CCK-OP group and of 13 patients in the soy-flour treatment group. Significant differences from pretreatment values (100%) are indicated as in Fig. 1.

Cumulative enzyme values are shown in Fig. 4. Lipase and amylase increases remained at the levels achieved by the two treatments. The cumulative augmentation of trypsin, however, was less than the sum of the increases seen at the end of the individual treatments. About a 20% decrease in trypsin augmentation was found at the examinations three months after both treatments, unlike the other enzyme values (data not shown).

Cumulative overall enzyme values did not increase in all cases; in three patients enzyme secretion deteriorated during the interval between the two treatments.

Subjective symptoms ameliorated during and after the treatments in almost all patients, as in our previous studies (5, 7). The patients' own evaluation of symptomatic changes focused on a comparison of the two treatments. For 9 patients, abatement of complaints was more satisfactory as a result of CCK-OP treatment, and for 4 patients soy flour was more effective. For 7 patients the two agents were equally effective.

Manifestations of acute pancreatitis caused by either treatment was not recorded, but during the interval between the treatments some relapse was suggested by the decreasing values of pancreatic function tests in 11 patients.

Discussion

We have demonstrated earlier the trophic effect of CCK-OP and soy flour treatment in chronic pancreatitis patients (5, 7). Both treatments resulted in the same increases in pancreatic secretions in different patient groups.

In the 20 patients participating in the study reported on here, the two treatments administered in random order were not equally effective. The soy flour course resulted in larger increases than did CCK-OP in trypsin and amylase secretion and in overall enzyme values. Augmentation of dose or prolongation of course was not found to be advantageous in our previous studies (5, 7); thus the effect of the treatments may be regarded as optimal.

The soy flour treatment resulted in overall increases in enzyme production and ratios of these increases that were similar to the results obtained in our earlier study of 34 patients (7).

However, the preponderant increase of trypsin and lipase secretion after CCK-OP treatment (5) was seen only in those patients who received CCK-OP drops first; in the other 10 patients there was almost no increase in trypsin and lipase values.

The results of Lundh tests and secretin-pancreozymin tests were similar, so possible changes in intestinal hormone release in general (4) did not influence significantly the results of the present study.

The cumulative secretory changes found by the Lundh tests represent both the long-lasting effect of the treatments and also the spontaneous course of the disease. Calculating from the sum of the overall results of individual treatments and from the cumulative values, the effect of course was superposed. The spontaneous decrease in enzyme output corresponding to the progressive course of the disease was 6%–15% during the 3-month period before the treatments began. It seems that progression of chronic pancreatitis may be slower by 2% to 3% after the treatments for some time.

The decrease in trypsin values during the first 3 months after the two treatments may be explained by a redistribution of enzyme ratios caused by dietary factors (9) and by substitution therapy (unpublished data).

One of the treatments was effective at least temporarily in all cases, but in 3 patients pancreatic secretion relapsed even below the pretreatment level during the observation period.

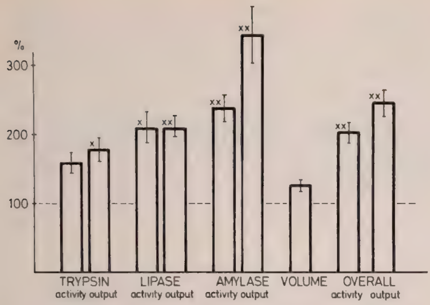

FIG. 4. Cumulative Lundh test results after CCK-OP and soy flour treatments. Percent changes of enzyme secretion from pretreatment values (100%) were calculated from Lundh test results measured after the second course. Significant differences from 100% are indicated as in Fig. 1.

Return to alcohol consumption (10), virus infection (11), and progressive arteriosclerosis (12) were thought to be etiological factors in the relapses.

The patients' subjective evaluation of the treatments was influenced by the special taste of soy flour and sometimes by fullness and bloating caused by the large doses. The fact that the acute secretory effect of intranasal CCK-OP is more effective (5) than that of soy flour (13) may have influenced the patients' subjective choice of CCK-OP treatment. The later abatement of complaints paralleled closely the increase in pancreatic functional capacity.

In conclusion, the CCK-OP and soy flour treatments seem to supplement each other, and successive courses further augment the functional capacity of the pancreas. In relapsing patients, however, additional attention has to be paid to the prevention of etiological factors in pancreatitis.

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Prospects in Medical Care: Physicians, Patients, Practice

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It is not self-evident why an economist, even one interested in health economics, should participate in the investiture of a professor of orthopedics into a named chair at a major medical school. However, those who know of the continuing dialogue about physicians, patients, and practice that Bob Siffert and I have carried on for the last quarter century in New York City and on Martha's Vineyard will recognize this address as the latest round in our discussions.

Physicians

The first point on my agenda this time is that we are going to have many more physicians in the next decade or two, but I question whether patients will therefore have greater opportunity to discuss their problems with them. Patients are likely to be treated more intensively and subjected to more procedures. By the end of this century, which is not very far away, there will be twice the number of physicians per thousand in the population than there were in 1950, a time when practitioners could not keep up with the demand for their services. And remember, even then people were not dropping dead on the street from lack of access to physician care.

The second point concerns the redistribution of physicians to smaller communities, which will have a serious impact on academic health centers and their major teaching hospitals. My friend Francis Moore, professor of surgery emeritus at Harvard, has estimated that by the year 2000, surgical specialists will be practicing in every hamlet with a population of five thousand. It is interesting to speculate what the big centers will do when that happens. On Martha's Vineyard, quite a small island, where I summer, I have observed a steady inflow of specialists over the past years.

At a recent conference of the private sector at Duke Medical Center, Dr. James Sammons, the executive vice president of the American Medical Association, warned that we are about to encounter a new crisis in medical malpractice. He anticipated that by 1986, surgical specialists would have to pay a premium of some $45,000 for malpractice coverage. (I do not think there is such a thing as "private-sector medicine." The government and insurance pay for 70% of all medical care. And government pays for most medical research and a large part of medical education. Private-sector medicine is more theory than fact.)

Hospitals are increasingly vulnerable to malpractice suits. I recently spent a day in Nashville with the Hospital Corporation of America. A verdict had just been handed down against them for $7 million in a case involving a physician whose appointment was under the control of his peers. The hospital had permitted the physician, supposedly a recovered alcoholic, to rejoin the staff. They considered him cured. Unfortunately he was not, and he seriously mismanaged a delivery.

Next, more and more students will graduate from medical school with debts of $100,000 or even $200,000. That will be quite a burden in a world in which more and more physicians will have to accept salaried positions because there will not be room for all to enter a lucrative individual or group practice. A salaried position will suit many physicians, including many women, who prefer a nonentrepreneurial form of practice,

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Professor Ginzberg is Director of Conservation of Human Resources, Columbia University, New York, NY. He delivered this paper on the occasion of the investiture of Dr. Robert Siffert as the first Robert Lippman Professor of Orthopaedics, The Mount Sinai Medical School, 5 May 1983.

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but it will not be satisfactory for those having large debts to liquidate.

Finally, with respect to the future income of physicians, let us remember that the President of the United States in his budget proposal has recommended a freeze on physicians' fees for Medicare and Medicaid patients in the coming year. The proposal will probably not pass. Nonetheless, it may pass next year or the year thereafter, even if a Democrat should be elected in 1984.

Patients

What changes are likely to occur on the patient front? First, I do not believe that the elderly or, as they are sometimes called, the frail elderly, will keep physicians and hospitals working overtime. To assume that is a demographic miscalculation. It is true that we will have more elderly, and more of the elderly will live longer and become increasingly frail. But not until the year 2010 will the country experience a significant rise in the elderly population. In that year, the members of the post-World War II baby boom will begin to reach 65. Between now and then lies a period of 27 years, and in the interim the numbers of elderly will increase, but they will not swamp us.

Next, despite the multiple criticisms leveled at American medicine, patients, according to the opinion surveys, continue to be satisfied with the health care they receive and especially with their relationships with their physicians. Of course, some are dissatisfied, some even sue. Although the public complains about high costs, most persons are protected by insurance. The key point is that the vast majority of the American public believes that it is well treated by its physicians.

But changes are occurring. The public is better educated and the media carry increasing information about the latest developments in therapy. Patients no longer accept uncritically what their physicians recommend, not even when the physician is a recognized specialist. More and more frequently, patients insist on playing a part in the decision-making process. Physicians are no longer permitted to diagnose and to prescribe unchallenged. Moreover they are beginning to recognize that since different patients have different value systems and different attitudes toward risk, pain, immobility, they, the physicians, must learn to match medical advice to the preferences of their patients.

Patients' perceptions, too, are changing. A recent report calls attention to the fact that two-thirds of the American public believes that it is right and proper to remove patients from life-maintaining supports if the prognosis indicates that they are unlikely to regain functionality. The major responsibility for making the decision to discontinue treatment, it is believed, should rest with the patient or the family. The public does not want physicians to decide; they do not want the clergy to decide; they do not want the courts to play a role. They view the decision as a patient-family issue. Clearly there are dangers if we advance too fast and too far in this direction, but the public is ready to move.

Imbedded in these changing views about life-support systems and death is the growing perception of the public—and I suspect that the public is ahead of the medical profession—that the prolongation of life is a relevant criterion by which to determine the choice of therapeutic procedure only to the extent that the quality of the patient's future is factored into the equation. The great contribution of orthopedics is not that it has prolonged life but that it has done so much for so many in improving the quality of their later years.

Practice

What about prospective changes in practice? First, we are now seeing the introduction of many new health-care delivery systems—more classic HMOs, more varieties of independent practice associations, new preferred-provider organizations, "surgi-centers," "emergi-centers," hospital-physician consortia, and other innovations.

On a recent visit to the Mayo Clinic, I was approached by two physicians from St. Paul who were participating in a postgraduate course. At the end of my talk they asked, "Do you think there is any future for the private practice of medicine? Every week in the Twin Cities we have a new HMO or something similar starting up which is threatening us." I attempted to reassure them that their practices would not be in serious jeopardy for many years.

Nevertheless, I expect that the people who pay the bills will have an important role in reshaping the system. Recently, the papers carried the announcement that the governor of New York, in collaboration with the mayor of New York City, had decided to restrict the freedom of Medicaid patients to choose their physician. Henceforth they will have to obtain their care from providers designated by the City. Insurance policies for middle-class persons are being rewritten to influence their choices, usually by monetary incentives. If they opt to have certain procedures performed on an ambulatory basis, their policy will cover 100 percent of the cost; otherwise, they will be liable for 20 percent.

In 1965 we linked health-care delivery in the United States to the U.S. Treasury, and from that day to this the Treasury has been pumping dollars into the system. But no industry or activity can look foward to a permanent favored relationship with the U.S. Treasury, not even the Department of Defense, as President Reagan and Secretary Weinberger are discovering. The President wants increased co-payments by Medicare patients. Moreover, DRG-based reimbursement, aimed at reducing the costs to government, is on the horizon.

The head of Massachusetts General Hospital, Dr. Robert Buchanan, told me that within a single week three large insurance companies approached him to ask whether MGH would become the preferred provider. They were looking forward to selling some new policies. The marketing era in health care has arrived!

The reason is clear. The era of open-ended governmental underwriting of costs is coming to a halt. The new system of prospective reimbursements will surely not work as anticipated, not the first or even the second time round. But the federal government has no option but to make it work. It cannot validate all bills that are submitted. Consider the budget forecast for 1995: the Medicare trust fund will be about $300 billion short. That is a prospective deficit that requires more than cosmetic attention.

Moreover, the newspapers are calling attention to the large numbers of the unemployed who have lost hospital coverage for themselves and their dependents, usually thirty days after the loss of their jobs. The best current estimates are that 4 million workers and 6 million dependents do not have hospital insurance.

In the meantime, Massachusetts is reimbursing its hospitals one way, New York State is going down a somewhat different track, and California, as might be expected, is buying care for Medicaid patients at the lowest bid. It is lucky that California is in the Union because the rest of us can find out at no cost to ourselves what does *not* work.

I conclude, then, that the golden age of American medicine, defined in terms of a prolonged period of prosperity for its practitioners, is coming to an end.

Since 1965, physicians have been paid for everything they do, even for putting their heads into a patient's room to say, "Good morning." Private treatment of the poor at no charge or for reduced fees, as well as the unrequited service they performed for ward and clinic patients, ended in 1965. But the imminent severance of the link between the health-care system and the Treasury presages the end of prosperity for the medical profession.

Second, hospitals are going to face increasing pressure because the demand for hospital care has leveled off and, as I suggested earlier, the frail elderly will not close the gap, surely not if more co-payments are required from them.

Third, graduate medical education, to which this and other major teaching hospitals have been major contributors, has no independent financial base. Patients pay for graduate medical education. It is an unusual way of doing things, but that is the way the system evolved. The costs for residents, for teaching, for research, are added to the patient's bill. Up till now, government and insurance have been willing to cover these charges.

But the critical question is how much longer they will agree to do so. I suspect that it will not be very long. In Massachusetts many of the leading teaching hospitals, when confronted with the new three-year constraint on reimbursements, had to take early action to cut back on residencies. It is no secret that the issue has surfaced in Albany. And to make matters worse, within a year or so we may have more graduates from U.S. medical schools than approved first-year residency positions. If that happens, chaos may result.

In my youth, medicine and economics were closely linked. Every physician made medical decisions with an eye on what the patient could afford, on what community resources, underwritten by philanthropy, were available. The break in this essential linkage started with insurance and was completed by Medicare and Medicaid in 1965. Now we are relearning a lesson we never should have forgotten: it is never possible to disassociate any social activity from the availability and cost of the resources required.

My economist colleagues are talking only to themselves when they contend that the United States cannot afford to spend more than 10% or 11% of its GNP on health care. Of course it can, and I believe it will. But at some point, when the cost of medical care has risen to between 13% and 16% of GNP, the citizenry will decide that enough is enough. Medical care is not that expensive: it is dying care that must be restrained. My guess is that it soon will be.

And as we move in that direction many hospitals will disappear, many physicians will be less affluent, and many patients will experience some reduction in their freedom of choice. But none of these changes need be a calamity. They need not alter in any fundamental way the potential of American medicine to contribute in the future, as it has in the past, to the well-being of all Americans.

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Effects of Antithymocyte Serum on Cardiac Allograft Survival in Thymectomized-Splenectomized Rats

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ABSTRACT

The effect of three different regimens of rabbit antirat thymocyte serum (ATS) was investigated in the thymectomized-splenectomized rat. The experimental system was the heterotopic cardiac allograft in the LEW rat. ACI rats were used as donors. As previously shown, combined thymectomy-splenectomy had no effect on ACI graft survival. Combining the lymphoid ablations with a postoperative ATS regimen resulted in a prolongation of graft survival (mean, 19.8 ± 2.3 days) indistinguishable from the survival periods obtained in normal intact controls receiving only posttransplant ATS (22.0 ± 11.1 days). Graft survival was improved in some animals receiving the same total ATS dose divided between the pre- and posttransplant periods. Results in this experimental group, however, were scattered (range, 16 to more than 120 days; median, 37.5 days) and not significantly different from the results of the previous group. In contrast, thymectomy-splenectomy combined with a pretransplant regimen of ATS led to virtually permanent graft survival (well over 120 days) in all the experimental animals tested. Skin graft experiments together with mixed-leukocyte and ConA reactivity tests suggest that the operational tolerance in this group is attributable to a nonspecific depression of alloreactivity rather than to active suppression.

Previous studies from our laboratory on the effects of ablation of lymphoid organs showed that neither splenectomy nor thymectomy, nor their combination, was of any consequence to the survival of the ACI cardiac grafts in LEW rats. The impact of either procedure was not increased by the pretransplant administration of the gammaglobulin fraction of horse antilymphocytic serum (1). While pretransplant antilymphocytic globulin treatment was quite ineffective in delaying rejections in thymectomized (THX) or splenectomized (SPLX) animals, it had a remarkable effect in animals which had undergone combined splenic and thymic ablations. Thus, THX-SPLX animals which had received a pretransplant course of antilymphocytic globulin injections carried well-functioning ACI grafts for over 120 days without further posttransplant treatment (1).

The purpose of the present study was threefold. First, we sought to confirm our studies by using commercially available antithymocyte sera (ATS) in order to show that the above results were not due to a peculiar activity of the antilymphocytic serum globulins used in previous experiments. Second, we aimed at studying the effects of the timing of the ATS administration to determine whether pretransplant administration was the sole and the most rational way of employing such reagent. Last, we sought to investigate the mechanism of the operational tolerance observed in this model.

Materials and Methods

Male LEW rats (300 g) (M. A. Bioproducts, Walkersville, Md) were used as recipients throughout these studies. Male ACI (Lab. Sup-

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plies, Indianapolis, Ind) and BN rats (M. A. Bioproducts) were used as organ or skin donors.

Rabbit antirat thymocyte sera were purchased from a commercial source (M. A. Bioproducts) and were administered according to the regimens specified below.

Surgical Procedures. Thymectomy was carried out as described in (2). Splenectomy was performed according to a standard procedure. Thymectomy and splenectomy were carried out the same day. Heterotopic cardiac grafting was carried out as described in (3). Cardiac grafts were monitored by palpation through the abdomen. Cessation of ventricular contractions was taken as complete rejection. Skin grafting was performed by suturing 2 cm^2 full-thickness grafts onto prepared beds on the back of the recipients. Discoloration, loss of pliability, shrinkage and appearance of necrotic foci were the parameters evaluated in judging rejection.

White blood cell counts as well as differential counts were done by standard hematological techniques.

Cell Cultures. One-way mixed leukocyte reactions (MLR) were performed with peripheral blood mononuclear cells isolated by centrifugation on Ficoll-Hypaque density gradients. These cells were then washed with 10% fetal calf serum in RPMI 1640 and resuspended in medium consisting of RPMI 1640 with 25 mM hepes, 10% fetal calf serum (Rehatuin, Reheis, Chem. Co., Kankakee, Ill), 2.5×10^{-5}M mercaptoethanol, 300 μg/ml of fresh glutamine, non-essential amino acids, and antibiotics. Responder cells (10^5) in 0.05 ml were plated in round bottom plates (Costar #3799; Costar, Cambridge, Mass). Stimulating cells (2×10^5) treated with Mytomicin C (50 μg/ml 30′, 37°C) were then added in a volume of 0.1 ml of complete medium. After an incubation of four days in a humidified atmosphere of 5% CO_2 in air, cultures were pulsed with 1 μCi of tritiated thymidine (20 Ci/mM) and harvested four hours later.

Mitogen stimulation was carried out using peripheral blood mononuclear cells. One $\times$ 10^5 cells in a volume of 0.1 ml were plated in round bottom plates (Microtiter: Dynatech, Alexandria, Va). ConA (Boehringer-Mannheim, Indianapolis, Ind) was added at a final concentration of 1 and 5 μg/ml, and plates were incubated for 72 hours. Cultures were then pulsed with 1 μCi of tritiated thymidine and harvested four hours later.

Experimental Protocol. Experimental animals were divided into three groups.

Group 1: Posttransplant ATS. Recipients in this group were thymectomized, splenectomized, and grafted on the same day. ATS administration was started on the day of transplant at a dose of 1.5 ml IP. A total of eight doses was administered on alternate days.

Group 2: Pre- and posttransplant ATS. Recipients were thymectomized and splenectomized and received the first injection of ATS on the same day (1.5 ml IP.). Three additional doses were then administered on alternate days prior to cardiac grafting which was carried out one week after the last injection of ATS. Four additional doses of ATS were administered on alternate days starting on the day of transplant.

Group 3: Pretransplant ATS. Following thymic and splenic ablation, rats received a total of six to eight doses of ATS over two to three weeks prior to transplantation. Recipients were given transplants seven to ten days after the last injection. No further treatment was given posttransplant.

In all these groups, the ATS effect was monitored by WBC and lymphocyte counts. ATS administration was delayed or stopped in individual animals whose WBC counts fell below 5000 cells/mm^3. Transplantation was delayed accordingly.

Statistics. Statistical evaluation of the data was done by the Wilcoxon rank-sum test.

TABLE 1

Allogeneic Skin-Graft Survival in LEW Rats Carrying Long-term Surviving ACI Hearts

Rat No.	Skin graft survival (days)	
	ACI	BN
3	>100	>100
7	>100	>100
9	>100	14
1A	24	15
5A	24	>100
7A	16	16
9A	24	>100
Controls	8,8,8,8,9,9,10	8,8,10,10

Recipients were TH(X)-SPL(X) and treated with ATS prior to cardiac grafting. No treatment was administered prior to or after skin grafting.

Results

Effect of Posttransplant ATS. Graft survival in this experimental group was significantly higher than in THX-SPLX controls which received no ATS (19.8 ± 2.3 vs 6.5 ± .5 days; $p <$ .001). Intact control rats receiving only posttransplant ATS had, however, graft survivals statistically indistinguishable from the experimental group (22.0 ± 11.1 days).

Effect of Pre- and Posttransplant ATS. A proportion of the grafts in this group lasted consid-

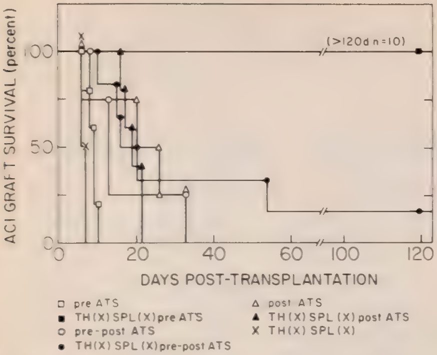


FIG. 1. Survival curves of ACI cardiac grafts in TH(X)-SPL(X) rats treated with posttransplant, pre- and posttransplant, or pretransplant ATS. Intact controls received ATS according to the same schedule.

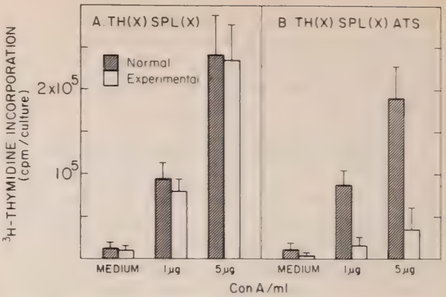


FIG. 2. Mitogenic response of PBL obtained before (**panel A**) and after (**panel B**) ATS treatment of TH(X)-SPL(X) LEW rats.

erably longer than in the previous group (Fig. 1). The overall results, however, were scattered (median, 37.5 days; range, 16 to more than 120 days) and statistically nonsignificant when compared to the posttransplant ATS regimens. One rat of 8 died of intestinal obstruction 12 days posttransplantation, and a second died of a pulmonary infection 17 days postgrafting. Both had functioning grafts but were excluded from statistical evaluation.

Effect of Pretransplant ATS. As in previous experiments (1), pretransplant ATS had a dramatic effect on graft prolongation in THX-SPLX rats (Fig. 1). All grafts lasted well over 120 days with excellent function. No rats were lost in the posttransplant period. Considerable care was exercised in the pretransplant monitoring of WBC and lymphocyte counts in this group, since sharp drops in counts occurred following the third or fourth ATS injection.

Specificity of Graft Prolongation in Pretransplant THX-SPLX Rats. The specificity of graft survival was tested by skin grafting. Thus, ACI and BN skin were grafted at the same time onto rats carrying long-term surviving ACI hearts (see Table 1). Both ACI and BN skin grafts were prolonged to roughly equal extents, strongly suggesting the lack of a specific mechanism in the survival of ACI hearts. No cardiac grafts were lost even in animals which rejected skin grafts.

Effect of THX-SPLX and Pretransplant ATS on ConA and MLR Reactivity. These experiments were performed as a counterpart to the skin grafting experiments to study (a) the impact of combined thymectomy and splenectomy with ATS treatments on cellular responsiveness and (b) the possible mechanism of the observed operational tolerance. To this end, experimental rats were tested after thymectomy and splenectomy, after this surgery and ATS treatment, and posttransplant. Normal rats were used as controls.

Thymic and splenic ablation had no effect on ConA reactivity (Fig. 2, panel A). In contrast, the response to the mitogen was drastically reduced in THX-SPLX rats following ATS treatment (Fig. 2, panel B). These results were paralleled by the MLR reactivity. As in the case of the response to ConA, thymectomy with splenectomy had no effect on MLR reactivity tested two weeks after this surgery (Fig. 3, panel A). But ATS treatment combined with thymectomy and splenectomy resulted in a considerable nonspecific loss of in vitro alloreactivity (Fig. 3, panel B). Such diminution remained unaltered in the postoperative period as shown by the low anti-ACI and anti-BUF MLR response of rats carrying functioning ACI hearts for more than 100 days (Fig. 4, panel A). This loss of reactivity does not appear to be due to active suppression, since peripheral blood mononuclear cells from these rats did not inhibit the MLR

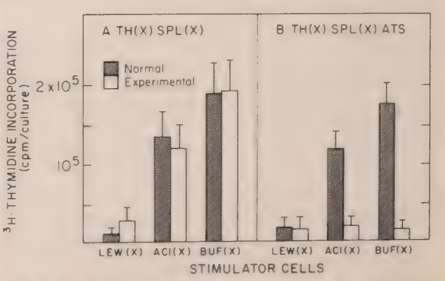
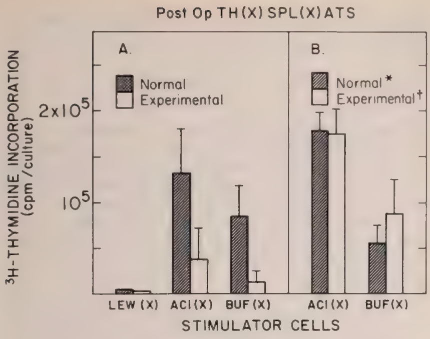


FIG. 3. MLR response of PBL obtained before (**panel A**) and after (**panel B**) ATS treatment of TH(X)-SPL(X) LEW rats.



* PBL + Normal PBL (My)
† PBL + Experimental PBL (My)

FIG. 4. **Panel A:** Posttransplant (100 days) MLR response of PBL from TH(X)-SPL(X) LEW rats treated with ATS prior to transplantation. **Panel B:** MLR response of normal PBL mixed with Mytomicin-C–treated PBL obtained 100 days posttransplant from TH(X)-SPL(X) LEW rats treated with ATS prior to transplantation.

when cocultured with such cells from normal controls (Fig. 4, panel B).

Discussion

Since their introduction by Woodruff and Anderson in the early 1960's (4), antilymphocyte sera have consistently been shown to be effective immunosuppressive agents in experimental transplantation (5). Over a decade ago, antilymphocyte sera were also reported to be immunosuppressive in humans (6, 7), but use of the sera in clinical transplantation is still controversial. Thus, while some groups have found antilymphocyte sera of value for the prophylaxis or treatment of rejection (8–10), others have reported contrasting results (11–12). The variability of the efficacy of the sera may stem from factors such as the potency and the source of the preparations, the timing and duration of the therapy, and the heterogeneity of the patient populations in terms of responder status and degree of priming. In addition, antilymphocyte sera have a complex mechanism of action (13) and may variably interact with other immunosuppressive treatments. Thus, several experimental studies as well as some clinical ones showed interaction of antilymphocyte sera with transfusions, immunosuppressive drugs, and lymphoid ablations (14–18), suggesting that these sera may have a significant role in combination therapies.

The results of the present study confirm and extend our experience on the interaction of antilymphocyte sera with thymic and splenic ablations and stresses the importance of the timing of the therapy. Thus, combined thymectomy and splenectomy in conjunction with pretransplant administration of ATS resulted in a state of operational tolerance characterized by long-term survival of ACI cardiac grafts in LEW hosts. These results agree well with our previous experiments in which we employed horse antilymphocyte globulins in THX-SPLX rats, and indicate that the source of antisera is not of critical importance. Indeed, three different lots of commercial rabbit ATS worked equally well in our protocol.

While the effects of prophylactic administration of ATS were quite remarkable in this model, a similar total dose divided between the pre- and posttransplant periods was clearly less effective. Posttransplant ATS in the THX-SPLX animals was an even less successful regimen leading to results indistinguishable from those obtained in intact control animals receiving only postoperative ATS. The vastly different outcomes of the pretransplant as opposed to the pre-post and posttransplant ATS regimens suggest that, in the latter two cases, ATS does not deplete alloreactive cells with a rapidity sufficient to thwart sensitization and the initiation of a rejection reaction. Spared alloreactive cells attacking the grafts and reaching the extravascular space may then be protected from the action of ATS, and this may ultimately lead to the rejection of the graft. The ATS effectiveness might also have been considerably diminished by phenomena of recruitment (19–21), which would tend to increase the circulating cell load. A suggestion to this effect comes from the fact the diminution of WBC and lymphocyte counts in the group treated with ATS posttransplant only was considerably less than in the other groups throughout the ATS treatment period (unpublished observations). The possibility that this phenomenon may be compounded by a diminished lytic effectiveness of ATS on alloreactive cells undergoing blastogenesis is unlikely since ConA-induced blasts are efficiently lysed in vitro by ATS in presence of rat complement (unpublished results).

In the group given ATS pretransplant, in contrast, the state of operational tolerance was achieved with ease and consistency in ten out of ten animals. The only necessary precaution was to adjust the total ATS dose and the timing of the individual doses to depress WBC counts to a level approaching 5000 cells/mm^3. Caution was exercised to avoid lowering WBC below this level since, in our experience, this entails an unacceptable risk of infections. With appropriate monitoring, however, all the experimental animals tolerated the treatment well and survived without apparent ill effects under conditions of normal husbandry.

With regard to the mechanism, the in vitro data as well as the skin graft data support the hypothesis that the operational tolerance observed in this model is due to a nonspecific depression of alloreactivity rather than to some form of active suppression. Thus, while combined thymectomy and splenectomy had no effect on MLR reactivity, a dramatic drop was observed following ATS treatment of THX-SPLX rats. Such loss of reactivity remained largely unaltered and nonspecific in nature in the postoperative period. The diminution of MLR reactivity was paralleled by a concurrent diminution of ConA reactivity. Cell mixing experiments also showed that peripheral blood mononuclear cells obtained posttransplant from experimental animals were unable to inhibit the MLR of normal cells against ACI and BUF cells suggesting the lack of a specific or nonspecific active suppression.

A corollary to these and our previous findings derives from the demonstration that only the combination of thymectomy and splenectomy with ATS treatment (or antilymphocyte globulin treatment) induces a useful reduction of alloreactivity. Thymectomy alone or splenectomy alone, even though combined with antilymphocytic globulin treatment, is ineffective in this regard (1). This finding suggests that the thymus and the spleen can independently offset the immunodepleting action of antilymphocytic sera in this experimental model. While the compensatory ability of the thymus was expected (22), the ability of the spleen to bolster cellular reactivity was in question since splenectomy affects humoral rather than cellular responses and has small or no effects on graft survival in experimental and clinical transplantation (17, 23–28). Nevertheless, the spleen has been shown to be a major site for the maturation of the post-thymic precursors of mature T cells (29) and to be very active in antigen trapping and T cell recruitment following a transplant (30); this suggests a significant, if not essential, role for the spleen in cellular responses.

In conclusion, the present study confirms our previous experiments and demonstrates, in addition, that only pretransplant ATS in conjunction with thymectomy and splenectomy provides a depression of alloreactivity sufficient to permit long-term survival of ACI grafts in the LEW rat. The resulting state of operational tolerance appears to be nonspecific and not mediated by active suppression.

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Feline Genitourinary and Systemic Circulatory Changes Due to a Vasopressin Hormonogen

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Abstract

We have studied the effect of a vasopressin hormonogen (Glypressin; tGLVP) on the myocardial, lingular, renal, adrenal, and testicular blood flow of 14 male cats. At a dose which had no effect on blood pressure or pulse rate, but which caused significant splanchnic vasoconstriction, a significant increase in renal blood flow was noted. This was most pronounced in the area corresponding to the renal cortex. There was no change in blood flow in other organs studied.

We conclude that in the cat this hormonogen, in doses which decrease splanchnic circulation, causes an increase in renal blood flow.

The therapeutic use of vasopressin (VP) to decrease splanchnic blood flow is attended by several complications. Potentially the most important is on the myocardium, where fall in cardiac output, arrhythmias, and frank infarction may occur. Coagulation may be compromised by increased plasminogen activation (1). Tachyphylaxis has been reported (2). VP has to be given by meticulous, continuous intravenous infusion.

Triglycyl lysine vasopressin (Glypressin, tGLVP) is a VP hormonogen. It has some advantages over the parent hormone and lacks some deleterious side effects. Administration is greatly simplified, for it can be given by intravenous bolus injection. Conversion to the active hormone occurs in vivo, resulting in controlled, sustained release by cleavage of the lysine side chain. At therapeutic doses, no cardiac or hematologic side effects have been reported. The intact molecule has no effect on smooth muscle, but doses of tGLVP equipotent to a therapeutic dose of VP have smooth muscle vasoconstrictive effects at 10 hours. We have reported the effect of this hormonogen, in detail, in decreasing splanchnic blood flow in the feline circulation (3). We report here the effect in cats of therapeutic doses of tGLVP on the myocardium, lingular, renal, adrenal, and testicular circulation.

Methods. A detailed account of our methods has been reported (3). Briefly, 14 male cats were studied under pentobarbital anesthesia. Baseline blood pressure and pulse rates were measured. Animals then received either 0.5 ml of normal saline (control group) or 10 μg/kg tGLVP in 0.5 ml normal saline (tGLVP was a gift from Ferring Pharmaceuticals, Malmo, Sweden). Blood pressure and pulse readings were repeated five minutes prior to death at 30, 60, or 120 minutes following drug administration. Blood flow was determined using the methods of Sapirstein (4). Animals received ^{86}RbCl 20 μCi/kg as a rapid intravenous bolus, and were killed one minute later with 1 ml KCl IV. Systolic arrest occurs within three to five seconds.

The anterior two thirds of the tongue, both adrenal glands, the urinary bladder, the left testicle, and the apex of the left ventricle, were re-

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TABLE 1

Changes in Feline Blood Flow Following Administration of tGLVP

	Control n = 6	tGLVP n = 6	Significance (Student *t*)
Myocardium	2.40 ± 0.04	2.21 ± 0.40	NS
Tongue	0.37 ± 0.08	0.18 ± 0.04	NS
Adrenal	0.10 ± 0.03	0.16 ± 0.03	NS
Kidney	7.17 ± 0.53	9.63 ± 0.78	<.02
Cortex	5.51 ± 0.30	8.24 ± 0.59	<.005
Medulla	1.26 ± 0.12	1.99 ± 0.21	<.05
Papilla	0.39 ± 0.04	0.67 ± 0.07	<.05
Urinary bladder	0.21 ± 0.04	0.14 ± 0.04	NS
Testes	0.03 ± 0.008	0.03 ± 0.0009	NS

Blood distribution expressed as %, cardiac output measured by ^{86}RbCl. Combined totals for 30–60 mins, 10 μg tGLVP kg wt IV.

moved, weighed in toto, and a weighed aliquot taken. Both kidneys were decapsulated and weighed. A wedge was taken from the left kidney, and bisected. One half was measured in toto to calculate renal flow. The other half was sharply dissected into three sections: superficial golden yellow for cortex, middle pink for medulla, and inner white for papilla.

Specimens were placed in the lower 2.5 cm of a 16 × 100 glass test tube and counted at 1.10 mEv in an LKB Ultra Gamma II Counter. Calculations were made from published formulas (1). Statistical analysis was by group Student *t* test. Results are expressed as blood flow/gm wet tissue as a percent of cardiac output.

Results. No change in blood pressure and heart rate occurred with the dose of tGLVP given. Changes which were noted in flow at 30 and 60 minutes were no longer present at 120 minutes. Because no significant difference in values was found, data from animals sacrificed at 30 and 60 minutes were combined.

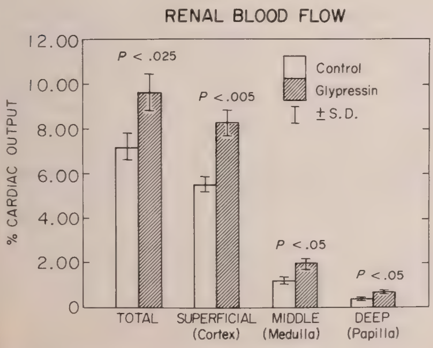

FIG. 1. Changes in renal blood flow following 10 μg Kg^{-1} tGLVP, combined studies for 30 and 60 minutes.

No changes were noted in blood flow through the myocardium, tongue, adrenal gland, and testicle (Table 1). However, there was a highly significant increase in the renal blood flow, which was most marked in the superficial area, corresponding to the cortex (Fig. 1).

Discussion. It is well established that some therapeutic doses of vasopressin may increase renal blood flow and urinary output (5). Furthermore, previous studies also showed that the increase in blood flow occurred without changes in blood pressure (6). This effect is dose-dependent. At higher doses of VP, renal blood flow falls (7). We have studied only one dose of tGLVP, and it was associated with a marked reduction in feline splanchnic blood flow but caused no change in blood pressure or heart rate (3). Extrapolation of these findings and dosages to other species should be done with caution. In this animal model, the desirable increase in renal blood flow has not been lost; moreover, splanchnic vasoconstriction has been preserved.

While this study did not address the antidiuretic effect of tGLVP, previous work has shown that it has a profile similar to VP (8). In addition, tGLVP increases hepatic arterial flow, which differs from findings on therapeutic doses of VP (3, 7). Recent studies confirm that tGLVP may be useful as a therapeutic replacement for VP (9).

The use of ^{86}RbCl as a blood flow marker is simple. However, in interpreting results, a caveat should be noted: ^{86}Rb, which is similar to radioactive potassium, diffuses across the cell membrane on the first pass. Thus, if circulation is stopped one minute following injection, measurements of the organs for radioactive content give accurate estimates of blood flow through the organs, excepting lung and brain (4). Blood flow is expressed as a percentage of cardiac output, not as an absolute value. The results are, therefore, ratios and as such do not reflect values which may occur as a result of changes in cardiac output.

We have compared blood flow in several species where different methods of determining blood flow have been employed (Table 2). Our study was performed on anesthetized animals, whereas those on humans, monkeys (10), and rats (11) were done on awake, alert subjects. The relatively decreased renal perfusion in our model may, to some extent, account for the subsequent elevation produced by tGLVP. The distribution of renal blood flow through the subdivisions were relatively crudely obtained. Yet they are not dissimilar to data from more precise studies, in which findings show that the juxta medullary cortex and outer medulla receive 20% of the cortical

TABLE 2

Percent Cardiac Output: Comparisons Among Species

	Human	Dog	Rat	Rhesus Monkey (sitting)	Cat
Heart	5.0	5	3.0	5.0	2.40
Stomach		3		1.0	2.25
Large & small intestine		15	19.0	8.0	18.85
Pancreas		2		2.0	9.93
Spleen		1	1.0	2.0	1.22
Portal	21.0	20		15.0	23.25
Hepatic (arterial)	6.0	10	7.0	5.0	11.69
Kidneys	23.0	11	18.0	12.0	7.17
Adrenals	0.5		0.2	0.1	0.10

Adapted from (4), (10), (11).

Values for humans using Fick principle; for rat, dog, cat using ^{86}RbCl; for monkey using microspheres.

blood flow (12). In this study, the medulla (middle) layer and the papilla (deep) layer receive 30% of cortical flow.

We conclude that tGLVP may have not only therapeutic advantages but hemodynamic advantages over its parent hormonogen vasopressin.

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Use of the One-Piece Shunting System in Adults

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Abstract

Five years of experience with the one-piece shunting system for the treatment of hydrocephalus are evaluated by two neurosurgeons in suburban practice. Advantages and disadvantages of the packaged, presterilized device and its instrumentation, as well as the low complication rate of the implantation procedure, are discussed. A series of 100 operations performed on 80 patients is presented.

The packaged presterilized one-piece shunting system was introduced at two suburban hospitals in January 1978. The previous series reported involved primarily infants with congenital hydrocephalus at a university center for pediatric neurosurgery (1). Our own study included adults with normal pressure hydrocephalus or hydrocephalus secondary to hemorrhage, infection, trauma, or intracranial tumor.

Methods. Eighty-seven primary shunting procedures were performed on 80 patients. Twenty-seven patients were diagnosed as having normal pressure hydrocephalus by both CT scan and radioisotope cisternography. Eighteen patients had hydrocephalus secondary to neoplasm, ten secondary to subarachnoid hemorrhage, and four secondary to bacterial meningitis. Fourteen patients developed posttraumatic hydrocephalus. Four patients with congenital hydrocephalus required removal of a blocked three-piece shunt and replacement by the one-piece system. Two patients had obstructive hydrocephalus secondary to aqueductal stenosis. One patient had recurrent bilateral subdural hematomas necessitating right and left subdural-peritoneal shunting. Two patients received left in addition to right ventriculoperitoneal shunts. Four patients needed a subdural-peritoneal shunt in addition to a ventriculoperitoneal shunt.

The packaging contained a 102-cm, spring-reinforced silastic tube with the slit valve set to open at a pressure of 5–9 cm H_2O. The ventricular end had 1-cm radiopaque markers up to 10 cm to assess the depth of insertion, while the peritoneal end had similar markers up to 20 cm. Enclosed were disposable 20-cm and 30-cm malleable shafts with plastic leaders and a single handle to facilitate grasping and guiding. A two-piece clip was provided to anchor and bend the tubing at the skull opening; there was also a one-piece clip to fix the shunt at the abdominal incision. A split ventricular cannula with a plastic obturator functioned also as a peritoneal perforator. Finally, a blunt needle was available to fill the tubing with saline solution to test the opening pressure of the shunt.

Shaving the scalp, chest, and abdomen was performed immediately after the induction of general anesthesia to avoid infection of superficial lacerations. All of the incisions were 3–4 cm in length and marked out with sterile indelible ink. The skin was scrubbed with povidone iodine solution. Sterile adhesive drapes were applied before the remainder of the table was draped with sterile sheets. Immediately prior to the first incision, 2 gm of methicillin was administered intravenously.

Attention was first directed to the right pari-

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etal area of the scalp. A curvolinear incision was made 6 cm posterior to and 6 cm superior to the external auditory meatus. Hemostats were placed on the galeal edges, and a self-retaining retractor was employed. Bleeding was further controlled with a bipolar forceps. After incising and scraping the periosteum, a burr hole was made with a hand drill; and the rim of the skull was coated with bone wax. The dura was coagulated with the bipolar forceps in a cruciate manner and opened with a number-11 blade. The pia-arachnoid was also coagulated with a bipolar forceps and opened with a number-11 blade.

The packaged blunt needle was inserted into one of the slit valves, and the shunt tubing was filled with saline in order to test the opening pressure. With the use of the 30-cm malleable shaft and its enclosed leader, tunneling in the subcutaneous connective tissue was begun at the scalp incision and continued inferiorly beyond the clavicle. As soon as the skin over the supraclavicular space was tented, a second skin incision was made to visualize the blunt tip of the leader. The guide-handle was removed, and the clasp at the other end of the leader was employed to bring the tubing to rest in the subcutaneous space.

One of the authors preferred to make the abdominal incision at McBurney's point, while the other made a linear incision in the right upper quadrant of the abdomen over the subhepatic space. Bleeding was controlled with the bipolar forceps. The guide and leader were used to pass the shunt between the supraclavicular and the abdominal incisions. A loop of tubing was left exposed over the clavicle for final adjustments.

Attention was redirected to the right posterior parietal area. With the use of the split cannula, the dilated ventricles were readily tapped. The ventricular end of the spring catheter was inserted through the cuff to a depth of 8 cm as soon as the plastic trochar was removed to prevent excessive loss of cerebrospinal fluid. The tubing was held in place with a blunt bayonet forceps while the cuff was removed and then anchored to the periosteum with the two-piece clip. Any slack in the shunt was adjusted by manipulating the loop over the clavicle and then eliminating the loop by gentle traction on the peritoneal end. Flow of cerebrospinal fluid through the shunt was verified before proceeding.

A self-retaining retractor was applied to the abdominal incision. The external fascia of the rectus abdominis was incised, and the muscle fibers were spread with a hemostat. The general anesthesia was then lightened in order to induce the peritoneal guarding reflex when the ventricular cannula was introduced. As soon as tightening occurred, the peritoneum was perforated. The plastic trochar was removed, and the distal end of the spring catheter was passed into the peritoneal cavity. The tubing was held in place with a blunt bayonet forceps while the cuff was removed and then anchored to the subcutaneous fascia with the one-piece clip.

In most cases, the authors were able to work independently on the ventricular and peritoneal ends of the shunt tubing, thereby shortening the overall operative time. All of the incisions were closed with nonabsorbable suture material. Methicillin 1 gm was continued intravenously every six hours until the patient was able to take nourishment by mouth. Prostaphillin 500 mg was then administered orally four times a day until the sutures were removed five to seven days later.

The patient was mobilized slowly over a five-day period to avoid sudden changes in intracranial pressure. When a left-sided ventriculoperitoneal shunt was required, the technique was essentially identical. If a subdural-peritoneal shunt was indicated, the distal end of the spring catheter including the slit valves was cut off prior to insertion into the periosteum in order to facilitate continuous emptying of the subdural collection.

Results. All of the patients were evaluated postoperatively by serial CT scans. Seven of the 87 primary shunting procedures (8.0%) required revision due to blockage of the distal end by omental fat or proteinaceous debris. Three shunts were irrigated with saline solution and reinserted into the peritoneum. The distal end was cut off in four cases and replaced with a medium-pressure Raimondi peritoneal catheter. All of the revised shunts remained patent.

Subdural collections occurred postoperatively in six of the 79 cases of hydrocephalus (7.6%). Two patients were followed by CT scan and treated conservatively. Two patients required craniotomy and drainage of a subacute hematoma and eventual insertion of a subdural-peritoneal shunt for a chronic subdural collection. Two patients developed large subdural hygromas and underwent early subdural-peritoneal shunting.

No primary wound infections were recorded in our total series of 100 shunting procedures. An 18-year-old man who underwent ventriculoperitoneal shunting for posttraumatic hydrocephalus needed a feeding gastrostomy; this was complicated by peritonitis; an ascending *Klebsiella* infection of his tubing necessitated two revisions and finally removal. A 48-year-old woman who required bilateral shunting procedures to relieve hypertensive hydrocephalus due to intracranial metastases ruptured a viscus because of intraabdominal metastases; the resulting infection of her tubing with mixed gram-negative organisms necessitated one revision and finally removal. A 67-year-old man who was shunted for normal-pressure hydrocephalus developed peritonitis following laparotomy for acute cholecystitis; an ascending *Pseudomonas* infection necessitated removal of the tubing.

Bleeding around the tubing in the right parietal area with some intraventricular leakage was observed on the postoperative CT scans of five patients, even though the tip of the catheter was correctly positioned within the ventricular system. Only one of the patients was symptomatic with fever and decreased level of consciousness for 48 hours. None of these shunts required operative intervention for drainage of a hematoma.

Discussion. Raimondi (1) conceived and introduced the one-piece shunting system to overcome and eliminate the major disadvantages of the three-piece shunt. The necessity of securing the three elements to each other risked inadequate connection by loose ligatures or cutting the tubing by tying the sutures too tightly. Subsequent disconnection allowed loss of shunt components into the ventricles or abdomen. The flow of fluid through the three-piece shunt with two connectors was not uniform due to changes in the inner diameter of the system, and the resulting turbulence and debris contributed to bacterial colonization. The flushing device did not provide reliable information concerning the functional state of the shunt. The frequent revisions that were required led to increased risk of infection. With the older device, when the peritoneal cavity was investigated as an absorptive site for cerebrospinal fluid, the direct insertion of an open-ended tube was associated with certain complications (2). Raimondi's (1) use of the distal slit valve to prevent insinuation of omentum, introduction of the split trochar for paracentesis to avoid surgical opening of the peritoneum, and design of a spring catheter to diminish kinking were innovations highly advantageous in treatment of newborns with hydrocephalus and children with myelomeningocele. All of these modifications in a 102-cm shunt were equally well suited to our own population of adult patients.

Obstruction of the ventricular end of the one-piece shunt was not a complication in our own cases, but 14 instances were recorded in Raimondi's (1) early series of 161 patients. Malfunction due to blockage of the peritoneal end was noted in 12% of Raimondi's procedures (1), compared to 8.0% in our series. Irrigation alone was successful in removing debris from three shunts, but the distal end of four shunts had to be cut off in order to restore patency. Since no spare parts were available for the one-piece system, attaching a medium-pressure Raimondi peritoneal catheter was considered preferable to revising the entire shunt and retapping the ventricle.

The overall incidence of infection reported by Raimondi (1) was 20%. No primary wound infections or bacterial ventriculitis occurred in our own patients. The regimen of antimicrobial prophylaxis suggested by Perrin and McLauren (3) was followed. Very low rates of postoperative sepsis have been reported for indwelling shunts with the use of prophylactic antibiotics (4).

Five cases of postoperative subdural hematoma were recorded in Raimondi's overall experience (1) with 457 patients, four in children over two years of age with closed fontanelles. The reported incidence of subdural hematoma following ventriculoperitoneal shunting in some series has been as high as 20% (5). Only two of our cases underwent craniotomy for removal of a subacute hematoma, but those patients and two others required subdural-peritoneal shunting for drainage of chronic subdural hygromas. Two additional asymptomatic hematomas were identified on follow up CT scan.

Summary. The one-piece design virtually eliminates the possibility of disconnection. The packaged, presterilized instrumentation facilitates rapid implantation. Lack of spare parts for revision can be overcome by catheter tubing and connectors already widely available. With regular use of prophylactic antibiotics, low rates of postoperative infection should be achieved. The few overall complications encountered in our series of 100 operations suggest that the one-piece system is highly adaptable to adult patients.

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Leishmaniasis

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Leishmaniasis is an endemic infection in Central and South America, Africa, southern Europe, the Orient, and the Middle East. Travelers who are visiting these areas may acquire the disease. The disease is caused by intracellular protozoan parasites of the genus *Leishmania* that are transmitted to humans by phlebotomine sandflies. A spectrum of clinical conditions may occur when humans are infected, varying from generalized visceral leishmaniasis to localized or disseminated cutaneous and mucocutaneous lesions.

Case Report

The patient is a 4-year-old boy seen in the Dermatology Clinic of City Hospital at Elmhurst, NY. He was born in Afghanistan. While the family was living in Pakistan, the boy's mother first noted that he had a generalized papular eruption, which lasted for 3–4 days and recurred every few weeks. From Pakistan the family moved to the United States (12 months prior to examination). Six months before coming to the clinic the boy developed a small papule on his right forearm which continued to grow in size and ulcerate. The mother reported that the boy was otherwise healthy. He had no systemic symptoms or underlying medical problems and had an unremarkable medical history.

The patient was an afebrile, well-developed, well-nourished boy. On the skin of his right forearm was a 5-cm circular lesion (Figs. 1, 2). This was a crusted violaceous plaque with central erosion and raised borders surrounded by small pustules. He had no lymphadenopathy or other abnormalities on physical examination.

Chest roentgenogram, complete cell count, and venereal disease reaction level were normal. Smear and culture for acid-fast bacilli were negative. Giemsa-stained smear was positive for abundant leishmanias intracellularly and extracellularly (Figs. 3, 4). Biopsy was positive for leishmanias. Culture was positive.

The patient was given no treatment for his disorder. He was followed up at approximately monthly intervals with continued improvement of his cutaneous lesions. Approximately 10 months after the first clinical sign of the disease, his cutaneous disease was completely resolved. A depressed, slightly violaceous scar had replaced the eroded, crusted plaque. The patient's general health continues to be good.

Leishmaniasis: Description and Classification

Organisms of the genus *Leishmania* exist in two forms: leishmanias (amastigote) in vertebrate hosts and leptomonads (flagellated promastigote) in invertebrate hosts and culture, both of which multiply by binary fission in their mammalian and insect hosts. In humans and other mammals, the rounded or oval amastigotes measure 4 × 2 μm and are usually found in the cells of the mononuclear phagocyte system but may also be seen in other peripheral blood leukocytes (Fig. 3). They multiply as small, rounded leishmanial forms 2–3 μm in diameter, containing a nucleus and kinetoplast, the pathognomonic Leishman-Donovan bodies. Multiplication of the parasite is exclusively intracellular in the mammalian host (Fig. 4). Continued intracellular multiplication of the parasite leads to rupture of the affected phagocyte and invasion of other cells, resulting in extensive histiocytic proliferation. When sandflies of the genus *Phlebotomus* obtain a blood meal from infected persons or animals, they ingest the amastigotes. In the midgut of the insect, these organisms change to spindle-shaped promastigotes which measure 17 × 3 μm. The promastigotes multiply, and within 4–5 days extend to the foregut of the insect. The promasti-

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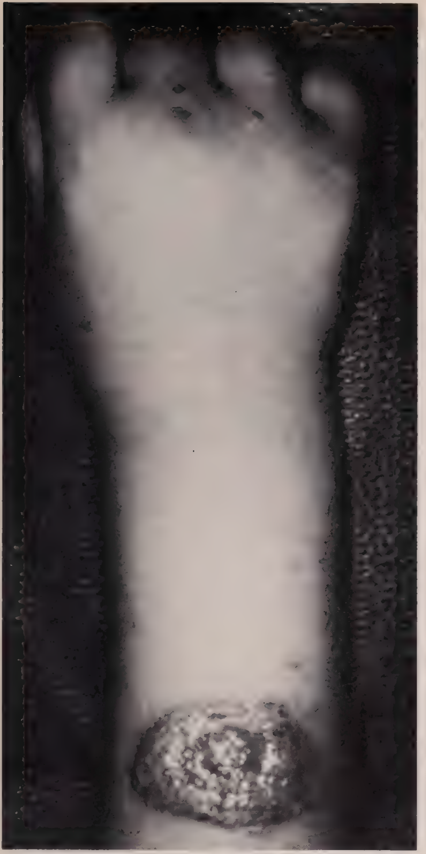

FIG. 1. Ulcer on the patient's right forearm.

gotes are transmitted to the mammalian host via the bite of the sandfly (1).

Leishmaniasis has been traditionally classified as follows:

- Visceral leishmaniasis, caused by *L. donovani,* occurring in both Old and New Worlds.
- Mucocutaneous leishmaniasis, caused by *L. brasiliensis,* occurring in the New World.
- Cutaneous leishmaniasis, caused by *L. tropica,* occurring in the Old World.

Morphologically, all species and subspecies of the genus are indistinguishable. They must be differentiated on biochemical, serologic, cultural, and behavioral grounds. Four main groups of *Leishmania* are currently recognized: *L. donovani, L. brasiliensis, L. mexicana,* and *L. tropica.* Each group contains a variety of strains that have been accorded separate species or subspecies status by some workers. A more detailed classification scheme is as follows (2):

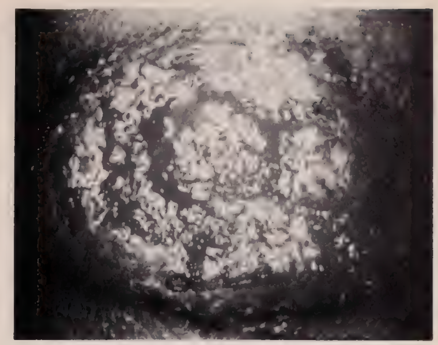

FIG. 2. Enlargement of Fig. 1.

- *L. donovani,* producing:
  - a. Kala-azar (visceral leishmaniasis)
  - b. Post-kala-azar dermal leishmaniasis or dermal leishmanoid
- *L. brasiliensis,* producing:
  - a. Mucocutaneous American leishmaniasis (espundia)
  - b. Cuntaneous American leishmaniasis (uta)
  - c. Disseminated anergic leishmaniasis (diffuse cutaneous leishmaniasis)
- *L. mexicana,* producing:
  - a. Chiclero's ulcer (Bay sore)
- *L. tropica,* producing:
  - a. Old World cutaneous leishmaniasis (Oriental sore, Delhi boil, Aleppo button, Salwk and Pendeh sore)
  - b. *L. recidiva* (leishmaniasis recidivans or tuberculoid form)

Leishmaniasis research today involves an investigation of its epidemiology as well as documentation of animal reservoirs and vector insects. The taxonomy of the group, the speciation schema, and the criteria used to define species have changed over the years (3). The epidemiology and clinical picture initially distinguished types. Subsequently, behavior in cultures and laboratory animals and data on the vector phlebotomines contributed to the classification. Current research concentrates on isoenzymes, the buoyant density of kinetoplastic DNA, and ultrastructural morphology of different species (4). Decisions about patient management must often be made in the absence of such information. Therefore, the following discussion of the diagnostic and therapeutic aspects of clinical leishmaniasis will concentrate on the three major clinical forms: visceral leishmaniasis, mucocutaneous leishmaniasis, and cutaneous or Old World leishmaniasis.

Visceral Leishmaniasis

Visceral leishmaniasis or kala-azar results from infection with *L. donovani* and is endemic in parts of China, the Indian subcontinent, the Mediterranean, east Africa, and South America. The description of the organism in kala-azar was detailed independently by Leishman and later by Donovan in 1903. Several hundred cases of visceral leishmaniasis have been reported in the United States: in troops returning from World War II, in immigrants from endemic areas, and in persons bitten by phlebotomine flies while traveling or living in endemic areas. Kala-azar is still often misdiagnosed. If a patient with intermittent fever, anemia, and marked hepatosplenomegaly comes from an endemic area, kala-azar must be considered.

Main Types. Visceral leishmaniasis can be classified into at least three main types even though the manifestations are basically similar. Variation in the strains of *L. donovani* in a given area and the length of time the disease has been endemic in a population contribute to the different manifestations (5).

Mediterranean, or infantile, kala-azar occurs in children under the age of 4 years, but may affect adults traveling to endemic areas. It is seen primarily in the Mediterranean area, China, Russia, and Latin America. Dogs, jackals, and foxes serve as reservoirs. Human-to-human transmission is rare. *L. infantum* and *L. chagasi* are the strains responsible for the Eurasian and American diseases.

Indian kala-azar affects older children and young adults. The human being is the only known reservoir; men are affected more than women. Antimalarial spraying has made this form of disease uncommon.

African kala-azar affects older children and young adults, like Indian kala-azar. It is found in the eastern half of Africa from the Sahara in the north to the equator in the south. It is endemic in gerbils and other rodents in many areas. African kala-azar is more resistant to therapy with antimony compounds than the other forms of visceral leishmaniasis.

Diagnosis. One rarely observes a primary lesion at the site of infection but minute papules have been described in infants. There are few phagocytosed parasites in the blood, but they are numerous in the reticuloendothelial cells of the intestinal mucosa, bone marrow, lymph nodes, liver, and spleen. The incubation period is usually 1–4 months, but may be longer (6). The initial fever is usually intermittent, with a daily rise to 102–104°C, and lasts for 2–4 weeks. Sometimes there is a pathognomonic double daily rise. Chills and sweating may be present, and the patient may present a malarialike picture; leishmaniasis is often confused with malaria. The differential diagnoses also include lymphoproliferative disorders, typhoid fever, tuberculosis, brucellosis, histoplasmosis, liver abscess, and leukemic reticuloendotheliosis.

Diarrhea may occur and is related to heavy intestinal infection. Despite these symptoms the patient has a good appetite and is usually ambulatory, but later sustains considerable weight loss and emaciation. The spleen gradually enlarges

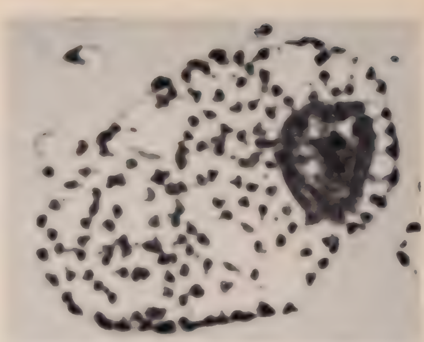
FIG. 3. Histiocyte filled with many *Leishmania*.

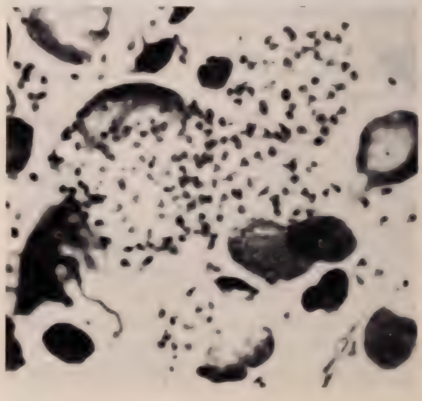
FIG. 4. Rupture of the affected phagocyte by continued intracellular multiplication.

due to the enormous increase of reticuloendothelial cells, many of them heavily parasitized. Similarly, the liver may be enlarged owing to proliferation of the Kupffer cells which contain parasites. SGOT is increased. Anemia, thrombocytopenia, and marked leukopenia with relative monocytosis and lymphocytosis develop. The anemia is due to reduced red-cell life-span and a mild degree of ineffective erythropoiesis (7). Plasma proteins undergo marked changes with a reversal of the albumin-globulin ratio, due largely to the elevation of the gamma globulins. This hypergammaglobulinemia is universally present. Proteinuria and hematuria are common in the course of kala-azar and are thought to be related to the glomerular deposition of poorly soluble immune complexes (8). Uremia due to renal amyloidosis and symptoms of heart failure can occur.

As the disease continues, skin changes develop. They may consist of darkly pigmented erythematous, granulomatous areas with numerous parasites, or hypopigmented areas with few parasites. In fact, kala-azar, meaning "black fever," acquired its name because of this patchy macular darkening of the skin due to deposits of melanin. These patches are most marked over the forehead and temples, periorally, and on the midabdomen (9).

General debility and leukopenia render the patient susceptible to secondary infections, for example, cancrum oris, noma, pulmonary infections, and gastrointestinal complications. The mortality of untreated kala-azar is 95% in adults and 80% in children. The untreated disease usually progresses to a fatal termination within 2 years. However, fulminating infections may cause death within a few weeks, and chronic infections may persist for years.

The diagnosis depends on the alertness of the physician to the possibility of the disease. Physicians should suspect kala-azar in a patient who has persistent irregular remittent fever, often with a double daily peak, leukopenia, and splenomegaly, who has traveled or resided in endemic areas.

Absolute diagnosis is made by finding the parasite in Giemsa-stained smears of the blood and tissues, culture, or inoculation of animals. In untreated patients the blood is usually examined first by smear or, preferably, by culture; if the result is negative, sternal, splenic, hepatic, or lymph-node punctures are performed. Splenic puncture reveals the highest percentage of positive findings. However, sternal or hepatic puncture are safer procedures. When the parasites are relatively few, multiple cultures of splenic or hepatic material in Novy-MacNeal-Nicolle medium containing 10% fresh rabbit blood give the most reliable results. The organisms usually grow in 7–10 days but cultures should be held for 3 weeks.

When parasites cannot be found, diagnosis may be made by complement fixation and indirect immunofluorescence antibody test. However, serologic tests are not totally satisfactory (10). The complement fixation test is sensitive and readily available but lacks specificity; cross-reactions may occur with the other human leishmanias and trypanosomes. Immunoelectrophoresis is highly specific but has low sensitivity. The indirect immunofluorescence antibody test is only group-specific. An enzyme-linked immunoabsorbent assay may be satisfactory. The leishmanin skin test is negative during active kala-azar but becomes positive several months after successful treatment of the disease. The intradermal Montenegro test is performed with a leptomonad suspension of 0.1–0.2 ml injected intradermally. The reading is made 48–72 hours later. A positive reaction is an area of induration 5 mm in diameter. The test is specific and sensitive, giving 95% positive results.

Treatment. Patients require rest, good diet, and treatment of complicating infections, which include tuberculosis, bacterial pneumonia, amebiasis, and bacillary dysentery. Pentavalent antimony compounds are highly effective against the parasite. Pentostam (sodium antimony gluconate) given intravenously or intramuscularly is the drug of choice (11). The adult dose is 0.6 gm (6 ml) for 6 days in Indian kala-azar; other forms require 30 days of treatment. Although the normal duration of therapy is 6–10 days, a shorter course may be administered to asplenic patients because of their enhanced response to treatment with Pentostam. Treatment for longer periods may be required in patients who respond slowly.

Relapses may occur up to 6 months after completion of treatment. Relapses occur in 5%–15% of African and Mediterranean cases. Patients should be retreated with three cycles of Pentostam for 10 days, each alternated with a 10-day drug-free period. Adverse effects of Pentostam therapy are infrequent and usually not severe. Nausea, vomiting, and abdominal pain may occur in 3%–10% of patients. Cough after injection is frequent. Uncommon adverse effects include pneumonia, transient albuminuria and mild hepatotoxicity, rash and urticaria, fever, chills, minor T-wave changes on electrocardiogram, epistaxis, sweating, and headache.

More than 90% of cases respond promptly to antimony. In Africa, however, the cure rate is as low as 70%. Amphotericin B or one of the more toxic diamidines can be used to treat resistant cases (12). Pentamidine is given intramuscularly, 4 mg base/kg dissolved in 3–4 ml water daily for 10 days. The course may be repeated twice after 10-day intervals. Hypotension, renal damage, hypoglycemia, and diabetes mellitus may occur.

Prevention. Important preventive measures include treatment of the disease in humans, elimination of diseased dogs, and use of DDT residual sprays against sandflies. The incidence of the disease has decreased in many areas where DDT has been used to eradicate malaria.

Leishmanoids. Cutaneous lesions called leishmanoids in which *Leishmania* organisms are demonstrable may develop in patients successfully treated with antimony compounds for kala-azar. These lesions are rare in Mediterranean or Chinese kala-azar but develop in 3% of African disease almost immediately after systemic symptoms subside (13). In as many as 10% of Indian cases, lesions occur after a latent period of 1–2 years. The cutaneous lesions may consist of hypopigmented macular lesions, erythematous papules, and confluent nodules. The hypopigmented lesions have decreased melanin in the epidermis. A mild cellular infiltrate of histiocytes, lymphocytes, and a few plasma cells appears in the dermis. Some histiocytes contain small numbers of *Leishmania*. The erythematous lesions also have decreased melanin in the epidermis, as well as more pronounced cellular infiltrate and a larger proportion of plasma cells than hypopigmented lesions. *Leishmania* are more numerous than in the hypopigmented lesions. The nodules, which are asymptomatic and rarely larger than 1 cm in diameter, occur predominantly on the face, involving the ears and mucous membranes, and to a lesser extent on the trunk and extremities. The nodular lesions show a compact cellular infiltrate of histiocytes, lymphocytes, and numerous plasma cells. Occasionally a few giant cells are present. The number of *Leishmania* within the histiocytes varies but some usually can be found (14). The lesions are of short duration in African kala-azar but may persist for years in the Indian variety, creating a persistent reservoir of infection. Post-kala-azar dermal leishmaniasis should be retreated in the same fashion as the initial illness.

Mucocutaneous Leishmaniasis

In Central and South America, *L. mexicana* and *L. brasiliensis* infections result in cutaneous ulcers that may spread to mucous membranes and cause severely mutilating facial lesions. In some areas 10% to 20% of the population is infected. Three autochthonous infections have been reported from Texas (15). Current classification schemes include four types, evidently due to different strains (16): chiclero ulcer, diffuse or disseminated cutaneous leishmaniasis, uta, and espundia.

Chiclero ulcer is found in Mexico, Guatemala, British Honduras, and other parts of Central America. The etiologic agent is *L. mexicana,* and the vector, a sandfly, *Lutzomyia flaviscutellata.* The disease occurs naturally in several arboreal rodents. The chiclero ulcer occurs frequently in workers who harvest chicle for chewing gum in the forests. The incubational period is 2–6 weeks. Three-fifths of the lesions are on the ear. The lesions on the ear usually run a long chronic course with little ulceration and few parasites; others undergo necrosis and mutilating cicatrization. The cutaneous lesions elsewhere on the body leave small scars after healing spontaneously within a few weeks. Mucosal ulceration does not occur. Ear lesions may cause extensive destruction of the pinna; these should be treated with a single 350-mg intramuscular dose of cycloguanil pamoate (17). Immunization with live cultures of *L. mexicana* has been effective in forest workers.

Diffuse Form. Convit and his associates described disseminated anergic American leishmaniasis (diffuse cutaneous leishmaniasis) in 1957 and continued to study this disorder (18–20). They considered this to be a variety of American leishmaniasis caused by several subspecies of *L. mexicana.* The disease begins with a single ulcer, nodule, or plaque from which satellite lesions may develop and disseminate to cover the entire body but without visceral involvement. The nasal mucous membrane is involved to a minor degree.

Current evidence supports the hypothesis that this disease results from a deficiency in the host's immune response. The course and appearance of the disease closely resemble lepromatous leprosy. The lesions contain numerous *Leishmania* and a moderate number of lymphocytes. The large number of *Leishmania* seen in routine stains facilitates differentiation of this disease. These patients have a specific anergy to the Leishman antigens. In contrast to other types of cutaneous leishmaniasis, the leishmanin skin test is negative. Diffuse cutaneous leishmaniasis is progressive and very refractory to treatment. Amphotericin B and pentamidine have been used to produce remissions, but cure is rare.

Uta. The lesions of the uta type are similar to those of the Chiclero ulcer except for less predilection for the ears. They rarely extend to the mucous membranes. Uta occurs in cooler, mountainous territories at elevations of more than 2,000 feet above sea level. It consists of single or multiple skin ulcers of the nose and lips. Parasites are readily demonstrable in these ulcers. Spontaneous healing occurs within 3 months to a year. The etiologic agent is *L. peruviana,* a member of the *L. brasiliensis* group, and the reservoir is the domestic dog. The disease has decreased greatly because of widespread use of insecticides in Peru.

Espundia. *L. brasiliensis* causes espundia in tropical Latin America. The organism is transmitted from large forest rodents to human beings by sandflies when new settlements are made in jungle areas. The initial skin lesion enlarges progressively and secondary bacterial infection is frequent. The primary cutaneous ulcer may be only the first phase of the infection, and hematogenous or lymphatic dissemination of the parasites can result in secondary mucosal involvement of the nasopharynx, causing severe facial mutilation. This secondary manifestation is known as espundia and is extremely difficult to treat. Mucosal complications are accompanied by fever, anemia, and weight loss. Destruction of the nasal septum produces a characteristic deformity called tapir nose or camel nose. The hard palate may be destroyed and laryngeal erosion can lead to aphonia.

Over 90% of the patients have a history of cutaneous leishmaniasis years before nasal involvement is discovered. The period between the first attack and the mucosal complications varies between 3 and 10 years (21). In blacks, the lesion is often hypertrophic, and large polypoid masses deform the lips and cheeks. This can be mistaken for South American blastomycosis.

The diagnosis is made by finding the organisms in scraping or by culture. However, isolation of the organism is difficult; it is not usually seen in direct smears and culture of biopsies of granuloma. Inoculation of the nose and feet of a hamster with a suspension of tissue triturated in saline may result in the development of a nodule within 6 months or a year from which few amastigotes can be recovered. Growth in culture is difficult to maintain. These biologic characteristics designate *L. brasiliensis* complex. The histologic characteristics show a poorly defined chronic granuloma with many lymphocytes and plasma cells; they are not diagnostic of the disease. The leishmanin skin test is positive in 90% of patients and is valuable evidence of infection. Weak antigens give false-negative results. Antigen must contain more than 1×10^6 promastigotes/ml, and a concentration of nitrogen of at least 30 μg/ml is desirable. In about half of the patients, the indirect fluorescent antibody test using an amastigote antigen is positive.

The treatment of choice for this infection is pentavalent antimony. However, disagreement persists on frequency of administration and dose. Amphotericin B is an effective alternative to antimony therapy and in cases resistant to antimony, it may be the drug of choice (22, 23). Dosage should be 0.25–1 mg/kg by slow infusion, daily or every other day, for up to 8 weeks. Even though the early lesions respond well, the mucosal complications of the espundia type heal slowly. The prognosis is poor in advanced cases.

Cutaneous Leishmaniasis

In Central Asia, India, the Mediterranean, and West Africa, *L. tropica* causes Old World cutaneous leishmaniasis or Oriental sore (Figs. 1–4), an infection of the skin which is usually self-limited. Borovsky, a Russian military surgeon in Tashkent, has been credited with the first description of the disease, in 1898. However, and earlier treatise on the subject was published by Altounyan in 1885, based on observation in the region of Aleppo, Syria (24). Rahim and Tatar attribute the first description of the disease to El-Razi in Iraq around the year 1500 (25). Old World cutaneous leishmaniasis is seen in the United States among travelers and immigrants. Hambrick and Even-Paz in 1966 reported three cases of cutaneous leishmaniasis caused by *L. tropica* encountered in Philadelphia in persons who had been to Israel (26).

Rural and Urban Types. The disease has been traditionally classified into rural and urban types caused by two strains of *L. tropica* (27).

The wet or rural type, caused by *L. tropica major,* has an acute course with early ulceration. It has its reservoir in gerbils and other small rodents. The ulcers usually appear on the extremities 2–6 weeks after the bite of the sandfly. Spontaneous healing usually takes place within 6 months, leaving a characteristic slightly depressed scar.

The dry or urban type, caused by *L. tropica minor,* runs a chronic course with late ulceration. Humans and the domestic dog serve as reservoirs of infection. The dry type develops much more slowly and heals more slowly than the rural. Incubation ranges from 2 months to a year. The lesion is usually facial and begins as a pruritic, purplish nodule (the Aleppo button) which slowly enlarges and finally breaks down after 3 or 4 months. Healing of the indolent, granulomatous ulcer may require a year or more.

Both types occur in the Middle East; both may infect the same person simultaneously. The urban form is prevalent in southeastern Europe, India, and North Africa; the rural in the remainder of Africa.

Diagnosis. The lesions begin as small 3- to 4-mm papules that progress to nodules that are red-brown and have a smooth surface. The lesion later extends peripherally and ulcerates centrally with the formation of a central crust. The hard excresence at the center of the granulating base of the ulcer is called the Montpellier sign or the rake; beneath this the parasites are likely to be found when scrapings are examined. The primary Oriental sore shows first an infiltrate consisting predominantly of large histiocytes filled with many *Leishmania* (28). In addition, lymphocytes and a few plasma cells are present.

Ulceration is produced by penetration of the basement membrane by the parasites and by the disintegration of the epidermis. When ulceration sets in, a secondary neutrophilic infiltration occurs. Leishmania organisms can be found extracellularly even though they are mainly present within histiocytes. The parasitized histiocytes measure 20–40 μm in diameter and may contain many *Leishmania* (Fig. 3). Older lesions gradually develop a tuberculoid infiltrate, with considerable diminution in the number of histiocytes. As the amount of histiocytes decreases, the number of organisms decreases correspondingly.

No organisms may be detectable in the final stage, so that the diagnosis can be made only by means of culture or skin testing.

A second phase, termed chronic leishmaniasis and characterized by small nodules, develops in some patients (29). The nodules appear while the ulcer is healing or, less frequently, some time after the ulcer has healed. The nodules of chronic leishmaniasis, or leishmaniasis recidivans, are brownish-red and often arranged in plaques. They have whitish scales with the apple-jelly characteristics of lupus vulgaris. They spread peripherally on a common erythematous base. Clinically the lesions greatly resemble those of lupus vulgaris, with a tuberculoid infiltrate that is often indistinguishable from that of lupus vulgaris. However, the sparsity of plasma cells in the inflammatory infiltrate and lack of caseation necrosis may help in the distinction. A few *Leishmania* can be found occasionally on careful searching.

Hart et al, in a report of a case of late cutaneous leishmaniasis, stated that the incidence of this disorder has been reported to be from 3% to 10% in patients with acute cutaneous leishmaniasis (30), and thought that the 3% incidence was probably more accurate. There is no evidence that treatment of acute cutaneous leishmaniasis decreases the probability of the development of late cutaneous leishmaniasis.

The diagnosis of Old World cutaneous leishmaniasis in endemic areas is not too difficult. In other localities, Oriental sore may be confused with syphilis, yaws, lupus vulgaris, and pyogenic granulomas. Diagnosis is usually made on clinical grounds and is confirmed by identification of the parasites.

Leishmania are seen best with Giemsa stain; with it the nucleus and the kinetoplast, which easily differentiate the organisms from other parasites, appear bright red. *L. tropica* can be cultured in Nicolle-Novy-MacNeal medium at room temperature to demonstrate leptomonads. *L. tropica* antigen skin testing becomes positive in the vast majority of patients with the disease as early as the second month and can persist for years. A positive reaction is characterized by a red area with a central papule that appears in 8–15 hours and reached a maximum in 48 hours. Positive reactions have been obtained in 93% of persons with established sores, in 98% of those recovered from the infection, and in 7–13% of those with no history of infection (31).

Even though the identification of the organisms in histopathologic sections of infected tissue has proved most useful, serologic tests add a new dimension to the diagnosis of this disease (32). Direct agglutination and IFA are still being evaluated. There is evidence of serologic cross-reactivity of the IFA and direct-agglutination test in the three leishmanial infections. A titer of 1:32 is considered positive and a titer of 1:16 borderline. The direct agglutination test measures primarily an IgM antibody level, which rises and falls quickly in the course of the disease.

Treatment. Many different modes of treatment for *L. tropica* infections have been suggested, including antimonial compounds and the antimalarials (the most widely used drugs); diamidines and sulfanilamides; Amphotericin B and other antibiotics; corticosteroid therapy and smallpox vaccination; surgical excision or treatment by physical means (radiation, electrocautery, and cryotherapy). None of these methods has proved to be an effective or superior treatment for Oriental sore.

Griffiths and Sodeify undertook to assess the value of metronidazole in southern Iran, an area endemic for Old World cutaneous leishmaniasis (33). All cases were confirmed cytologically by the finding of Leishman-Donovan bodies. In a double-blind trial involving antileishmanial regimes, they found metronidazole to have some effect on the lesions in only 6 of 24 patients; the improvement was not sufficiently marked to be of much benefit to the patient. They concluded that the two lesions that cleared completely did so spontaneously and that the six patients who did not reattend were more likely to have done so because there was no visible improvement rather than because they were cured.

The antimonials are the most frequently recommended drugs. They can have serious side effects, but the reported incidence of serious toxicity with the use of pentavalent antimony compounds is low. The toxicity of the other recommended agents, except for amphotericin B, is generally less than the antimonials.

Usually Oriental sore proceeds to complete healing. The infection sometimes, but not always, leaves disfiguring scars. Some of the recommended physical treatment modalities may themselves cause scarring. None of the treatments has been clearly shown to decrease scarring or alter the natural course of the disorder. There is no proof that treatment of acute cutaneous leishmaniasis decreases the incidence of the late chronic form. The lack of definite improvement, the toxicity of the drugs used, and the self-limiting nature of the disease have led some authors to suggest that the best management of uncomplicated cases of cutaneous leishmaniasis is to withhold treatment and observe the patient.

Rifampicin may offer the best chance for success in the treatment of Old World cutaneous leishmaniasis. Selim and Kandil in 1972 obtained good results with a daily dose of 1,200 mg Rifampicin; clinical healing occurred within 3–8 weeks (34). Mazzi in 1976 obtained clinical cure in one patient with a dose of 900 mg/day after 3 weeks (35).

In Iskander's 1978 study of the efficacy of Rifampicin (36), 13 patients were given 600 mg daily; 3 patients dropped out for reasons unconnected with the trial. Diagnosis depended on clinical appearance, identification of the organism in smears, and histopathology. No serologic tests were performed. Clinical improvement started after the second week of treatment. Of the 10 patients who continued treatment, 9 were cured with minimal scarring in 1–4 months. One patient was definitely improved after 1 month and was instructed to continue the treatment abroad. No unwanted reactions were observed clinically in these series.

Even-Paz et al in 1982 treated eight patients with cutaneous leishmaniasis with oral Rifampicin, usually either 600 mg or 1,200 mg daily for 28 days (37). In all cases, the diagnosis was based on positive smears or cultures. The sole criterion for healing was protozoologic negativity of both smear and culture, only if it occurred within 8 weeks after start of therapy. Of the 8 cases, 6 were treatment successes, 1 was a questionable success, and 1 a treatment failure. No adverse clinical or laboratory side effects were observed, except for diarrhea in one patient on the 27th day of treatment.

Prevention. Protective covering of the ulcers reduces the chances of transmission. Poisoning rodents in their burrows is effective in reducing human infection in nearby settlements. The incidence of Oriental sore has been reduced by insecticide spraying to control the sandfly population, but the extent and variety of sandfly habitat often makes spraying impractical. Screens and nets may protect humans from sandflies. Active immunization with living organisms provides effective protection, although immunity requires several months to develop. Cutaneous Old World leishmaniasis is followed by total immunity to the homologous strain. Vaccination has a centuries-long history in the Middle East. However, the experimental evidence for New World leishmaniasis suggests that strains causing limited cutaneous lesions do not protect against strains producing mucosal disease (38).

Available resources must be directed to the diagnosis, treatment, and prevention of infection by intracellular protozoan parasites of the genus *Leishmania*. Further studies of the value of serology in diagnosis and assessment of cure are crucial. Effective treatment with an inexpensive, nontoxic, orally administered drug is the greatest need.

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Tuberculosis Infection in Mount Sinai Medical Students: 1974–1982

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ABSTRACT

Medical students have historically been found to have a higher incidence of tuberculous infection and disease than the general population. An attempt was made to determine the risk of tuberculin conversion among students at Mount Sinai School of Medicine (CUNY). Between 1974 and 1982, 770 students entered the school; of these, 36 were tuberculin-positive. The tuberculin reaction records of the students who entered the school tuberculin-negative (734) were analyzed. There was a total of 1,568 person-years of surveillance among these students. Only two medical students converted from tuberculin-negative to tuberculin-positive. No student developed active disease. The rate of tuberculin conversion was calculated to be 0.13 conversions per 100 person-years of surveillance. This rate was less than that reported for the national and local general population. The risk of tuberculosis does not appear to be a significant health problem for medical students at Mount Sinai School of Medicine.

Introduction. Tuberculosis has for several decades been considered an occupational hazard for medical students. Many midcentury studies of this problem showed a much higher incidence of tuberculosis in medical students than in the general population. In 1946 Morris said, "tuberculosis control in medical students represents one of our grave modern medical problems" (1); in the same year Brean and Kane called tuberculosis "the most serious medical problem that confronts the medical student" (2).

Tuberculosis is still a significant national problem despite the precipitous drop in morbidity and mortality. In 1980, 27,749 cases of tuberculosis were reported to the Centers for Disease Control and almost 10% of these (2,294) were in the state of New York (3).

Physicians of every age have been reported to have tuberculosis infection rates more than twice the rates in the U.S. population of comparable age. At least half of this infection occurs after beginning medical school and is presumably hospital acquired (4).

Contracting tuberculosis during medical school is a concern of most medical students. This study attempted to determine the risk of acquiring tuberculous infection during medical school and to determine also whether tuberculosis remains a serious health problem among students at the Mount Sinai School of Medicine (MSSM) in New York City.

Methods. All Mount Sinai medical students are tested every year for tuberculous infection. The testing is done early in the first and second years of medical school and then in the middle to late part of the third and fourth years. PPD stabilized with Tween 80 is utilized as the antigen for testing. The standard Mantoux technique is used: 0.1ml of tuberculin containing 5 TU is injected intradermally into the volar or dorsal surface of the forearm and a wheal is raised. The test is read 48 to 72 hours after injection. A positive reaction is 10mm or more of induration; erythema is disregarded. This is the method recommended by the American Thoracic Society in 1981 (5). One of us

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(J.O.) administered the tuberculin tests from 1976 to 1982 and read all the equivocal and positive reactions. The tuberculin responses to the tests done in 1974 and 1975 were ascertained from the records kept by the previous Student Health Service nurse.

The tuberculin status of all the students in the classes of 1978 through 1984 was examined retrospectively in order to determine the rate and risk of conversion from tuberculin negative to positive among MSSM students.

The number of years that the students were under surveillance for tuberculous infection was then computed. Since the first PPD skin test only establishes a baseline, the years of surveillance were actually less than four for each student. The true period of surveillance was approximately three and one-half years for students who spent four years at MSSM, and one and one-half years for transfer students. In order to be conservative and to facilitate the calculations, the number of years of surveillance for each student was truncated to the lower number.

Results. The tuberculin reaction profiles of a total of 770 Mount Sinai medical students were analyzed from the classes of 1978 through 1984 for the years 1974 to 1982. Of these students, 643 spent all four years of medical school at MSSM and 127 transferred into MSSM at the start of their third year.

The 36 students who were tuberculin-positive by history or by testing during their first year, or had received a Bacillus Calmette-Guerin (BCG) vaccination in the past were subtracted from the total number of students in their class. This yielded 734 students who were tuberculin-negative upon entrance to MSSM (see table).

There was a total of 1,568 person-years of tuberculous-infection surveillance among the 734 students who entered MSSM tuberculin negative in the years from 1974 to 1982. Of the 614 person-years of student surveillance from the first to the second year of medical schooling, only one student converted from tuberculin negative to positive. No student converted in the period from the second to the third year (502 person-years of surveillance). There were 452 person-years of surveillance from the third to the fourth year of medical school, and one student converted to positive during this period. Both tuberculin converters were treated with isoniazid prophylactically and neither developed active tuberculosis. In addition, none of the 36 students who were PPD-positive on entering the school developed active tuberculosis.

Based on this relatively small sample and the very rare occurrence of tuberculin conversion, the rates of conversion at Mount Sinai School of Medicine during the period from 1974 to 1982 were as follows:

from year 1 to year 2:	0.16 conversions per 100 person-years of surveillance
from year 2 to year 3:	0
from year 3 to year 4:	0.22 conversions per 100 person-years of surveillance

This averages to a conversion rate for the three years of surveillance of 0.13 tuberculin conversions per 100 person-years of surveillance.

Discussion. Throughout this century medical students have been considered to be at greater risk of being infected by *Mycobacterium tuberculosis* than their counterparts in the general population. The decline in tuberculosis and tuberculous infection among medical students paralleled the substantial decrease in the general population since the turn of the century. Once one of the most feared of all diseases, tuberculosis is now a relatively rare, yet not insignificant problem.

All medical students are aware of their risk of being infected with *Mycobacterium tuberculosis*. Ward experience is commonly believed to give a student a greater chance of being infected than he or she would have if not in medical school. This study set out to determine the rate and risk of tuberculous infection in Mount Sinai medical students.

Surprisingly, only two Mount Sinai medical students converted from tuberculin negative to positive in the eight years from 1974 to 1982. The rate of conversion from tuberculin nonreactor to reactor for Mount Sinai medical students from 1974 to 1982 was 0.13 conversions per 100 years of surveillance. Another way to view this rate is that on the average 0.13% of students converted in any one year of medical school; or 0.51% of students on the average convert to positive, if they spend four years at MSSM. By the rate of conversion demonstrated by the classes of 1978 through 1982, only about one out of every 200 students who spend four years at MSSM will become tuberculin positive after entering tuberculin negative.

It is possible that some conversions in the senior years were missed by the method employed at the Mount Sinai Student Health Department. Fourth-year students receive their final tuberculin skin test in the middle or latter part of the year. Thus, there is a variable period during

TABLE
Tuberculin Conversion by MSSM Medical Students, Classes of 1978–1984

	No. of students		No. TB-positive on entrance		TB-negative on entrance			
Class year	Started at MSSM	Transferred	Started at MSSM	Transferred	No. Started at MSSM	No. Transferred	Years of surveillance	Tuberculin convertors
1978								
male	64	26	1	2	63	26	245	0
female	14	5	3	0	11	3		
total	78	31	4	2	74	29		
1979								
male	57	32	3	2	54	30	256	0
female	18	12	0	2	18	10		
total	75	44	3	4	72	40		
1980								
male	67	18	2	0	65	18	293	1
female	30	5	5	0	25	5		
total	97	23	7	0	90	23		
1981								
male	67	27	1	1	66	26	318	1
female	30	2	1	0	29	2		
total	97	29	2	1	95	28		
1982								
male	64	—	3	—	61	—	183	0
female	35	—	3	—	32	—		
total	99	—	6	—	93	—		
1983								
male	64	—	2	—	62	—	172	0
female	35	—	2	—	33	—		
total	99	—	4	—	95	—		
1984								
male	69	—	3	—	66	—	95	0
female	29	—	0	—	29	—		
total	98	—	3	—	95	—		
TOTAL								
male	452	103	15	5	437	100	1,568	2
female	191	24	14	2	177	20		
total	643	127	29	7	614	120		

which these students are still attending MSSM but are not under surveillance for tuberculous infection. In addition, there is a six to eight week lag period after an infection during which no tuberculin sensitivity reaction can be elicited. Therefore, surveillance for tuberculous infection for Mount Sinai medical students effectively ends six to eight weeks before the students' final tuberculin skin test. This means that for as much as one-half the final year at MSSM, presumably a period of high risk, the students are not under surveillance. If cases of tuberculous infection were missed during this period, the computed rate of conversion is obviously too low.

On the other hand, since the number of years of surveillance was truncated in doing the calculations, the period of surveillance was actually longer than that used in the calculation of the conversion rate. Thus the computed rate of conversion is slightly greater than the actual rate.

The medical literature since 1900 reports an extremely high rate of tuberculin positivity among medical students. Two studies which are most comparable to ours, one done in the late 1920s (6) and the other in the 1940s (7), both found an average conversion rate of 7% per year among medical students who were tuberculin nonreactors when they entered medical school.

It is now known, however, that the methods of tuberculin skin testing used throughout most of this century yielded a significant number of false-positive results, for three major reasons. First, old tuberculin was relatively impure and nonspecific for *Mycobacterium tuberculosis*. Second, the dose of tuberculin being used (often 250 TU) was far too large to be specific for tuberculosis. Third, the criteria for considering a reaction positive were too liberal. Therefore, many of the students considered to be infected with *Mycobacterium tuberculosis* may not have been truly infected.

The most comprehensive study in recent years was done by Barrett-Connor in 1979 (4). She stated that the conversion rate among medical students in the 1970s was 1% to 2% per year, and this was "at least twice the age-specific infection rate for the U.S. population as determined by the Public Health Service." However, Barrett-Connor considered many reactions positive that the Public Health Service (8) would have considered negative.

The rate of conversion found among Mount Sinai medical students was less than the rate reported in any previous study of medical students. There can really be no comparison to rates prior to the 1960s because today we have a far smaller incidence of tuberculosis and far more specific testing methods.

The rate of tuberculin conversion among Mount Sinai medical students should be greater than that of students at most medical schools nationwide because New York City has a very high relative incidence of tuberculosis. The percentage of New Yorkers who react to tuberculin rises steadily from the age of 16 to 52, at a rate of approximately 0.8% per year (9). This rate is much greater than the rate of 0.13% conversions per year calculated for students of MSSM. However, the fraction of Mount Sinai students who were nonwhite is far smaller than the fraction of New Yorkers who are nonwhite. This should lower the rate at MSSM relative to New York as a whole because nonwhites have a substantially higher rate of conversion than whites (9–11).

The only national estimates of the prevalence of tuberculin-positive skin-test reaction among noninstitutionalized American civilians ages 25 to 74 was provided by the National Health Survey published in 1978 (11). The skin testing was done from 1970 to 1971. The same testing method and criteria were used as at MSSM. The rate of tuberculin conversion among Americans aged 30 to 40 in 1971–2 can be approximated from the data to be 0.6% per year, 0.4% among men and 0.8% among women. This rate, too, is substantially higher than that found for Mount Sinai medical students. The relatively small percentage of women (28%) at MSSM will tend to skew the calculated rate of conversion downward, since women have a higher rate of conversion in the age group under consideration. It should be noted that the National Health Survey suffered from several difficulties related to small sample size, lack of response from the people sampled, and oversampling of the poor, which probably resulted in an overestimation of the prevalence of tuberculous infection.

The findings of this study should not be interpreted as meaning that routine tuberculin skin testing should be discontinued at MSSM. Early detection of tuberculosis infection in medical students is important for their health and for the health of the patients they care for.

The incidence of tuberculous infection among students at the Mount Sinai School of Medicine was extremely low from 1974 to 1982. It appears that the rate at MSSM is lower than the rates which have previously been reported for medical students. The risk of tuberculosis does not appear to be a significant health problem for medical students at the Mount Sinai School of Medicine.

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Splenectomy for Chronic Idiopathic Thrombocytopenic Purpura

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Abstract

A retrospective review of 69 consecutive patients who had splenectomy for idiopathic thrombocytopenic purpura between 1967 and 1980 is presented. Complete response occurred in 85.5% of the patients, partial response in 8.7%, and no response in 5.8%. The complication rate was 20%, and there were no surgical mortalities. Serious infections developed in 7% of the patients postoperatively. Initial platelet count, onset of disease, timing of splenectomy, and relapse rate were studied and found not to correlate.

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disease characterized by an autoantibody directed against normal platelets. In 1951, Harrington et al demonstrated that direct infusion of plasma from a patient with ITP into a healthy person resulted in a precipitous decrease in the platelet count of the healthy volunteer (1). Shulman showed that the factor producing the thrombocytopenia had characteristics of an antibody (2). Reproducible proof of the presence of an antibody was shown by Dixon and his colleagues in 1975 (3). Using an antiglobulin consumption assay, they were able to measure IgG on the platelet's surface.

Steroid therapy is the most frequent immunological manipulation employed in this disease. Although an initial increase in platelets is usual, approximately 50% of patients cannot maintain a normal platelet count upon tapering of the steroid dosage (4). Splenectomy has been the most effective treatment for chronic ITP. The reason for the success of surgery in raising the platelet count to normal levels is thought to be twofold. First, the spleen is the major source of antibody production (5). Second, the spleen is extremely sensitive to even mild antibody coating of platelets; therefore, platelets are destroyed on passage through the spleen.

The purpose of this report is to evaluate the efficacy of splenectomy for chronic ITP, the relapse rate, and the long-term effects.

Material and Methods. Between 1967 and 1980, 69 consecutive patients who underwent splenectomy for ITP were evaluated retrospectively. Sixty-six patients had the chronic type, and three had acute ITP. The duration of the disease prior to splenectomy ranged from 2 months to 18 years for the chronic form of ITP. All patients were operated on at The Mount Sinai Hospital, New York, NY.

The diagnosis of ITP was defined as (a) platelet count less than 100,000/mm^3, (b) normal or increased megakaryocytes on bone marrow examination, (c) absence of other known causes of thrombocytopenia, and (d) absence of splenomegaly, as measured by spleen weight at pathological examination, not by the clinical presence of a spleen tip on palpation.

Response to splenectomy was defined as "complete" if the platelet count increased to and remained above 150,000/mm^3 at six months postoperatively, as "partial" if the platelet count rose to at least 50,000/mm^3 but not more than 150,000/mm^3, and as "no response" if the platelet count did not exceed 50,000/mm^3 during the postoperative period.

Results. The 69 patients' charts available for review revealed a mean age of 38 years at the

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time of splenectomy (range 4–88 years). There were 46 women and 23 men. All patients were treated with high-dose prednisone for the initial management. The range of duration of steroid treatment prior to splenectomy was 3 days to 18 years, mean 25 months. All but one patient underwent elective surgery. The one emergency splenectomy was performed on a 19-year-old woman with an intracerebral hemorrhage. The three patients with acute ITP failed to respond to high-dose steroid treatment. Each patient developed significant gastrointestinal bleeding which prompted early splenectomy. The indications for splenectomy in chronic ITP were failure to maintain platelet counts above 100,000/mm^3 on reduction of steroids or failure of steroids to raise platelet counts to the normal range. There were no surgical mortalities.

Fifty-nine patients had a complete response in the initial postoperative period (85.5%). The mean preoperative platelet count in these patients was 57,700/mm^3, and the mean postoperative count was 420,000/mm^3. Six patients had a partial response, and four did not respond at all. The mean platelet count in this group of patients was 32,000/mm^3 prior to surgery, and 67,700/mm^3 postoperatively. One of the partial responders developed normal platelet counts six months after surgery. This patient had been on steroid therapy for twenty years prior to the operation, having refused surgery for that entire period of time. The in-hospital complication rate was 20%, which broke down as follows:

pneumonia	4
wound infection	3
bleeding	3
pulmonary embolus (no thrombocytosis)	1
fever of undetermined origin	1
subphrenic abscess	1
convulsion	1

Of the 60 complete responders, 41 were available for follow-up for a period ranging from 2 to 15 years (mean 10.5 years). Thirty-eight patients have maintained normal platelet counts, whereas three patients relapsed (5%). Relapse occurred at one, two, and five years postsplenectomy. The patient who relapsed at one year was treated with steroids and responded. It is now eight years post relapse, he is off steroids and maintains a normal platelet count. The other two patients have not responded to further management. All three patients had negative spleen scans for accessory splenic tissue.

Of the five partial responders, one was lost to follow-up. The four others have remained partial responders. Spleen scans have been negative in these patients also.

In the nonresponder group, postoperative spleen scan did not reveal any accessory splenic tissue to account for the lack of response to splenectomy.

Five serious infections developed in four patients. All four had splenectomy performed during adulthood. Two of the three patients who relapsed developed infectious complications, including bacterial meningitis and tuberculosis. Both responded to treatment. In the partial-responder group, one patient developed pneumococcal pneumonia and another developed meningiococcal meningitis and endocarditis. This latter patient died as a direct result of overwhelming sepsis. Two patients in the nonresponder group died as a consequence of continuing thrombocytopenia. Two other patients died six and ten years postoperatively from causes not related to either ITP or splenectomy. Postoperative thrombocytosis, defined as platelet count greater than 1,000,000, did not occur in any patient.

Discussion. Splenectomy significantly alters the course of ITP. This study confirms the findings of other large series that a sustained complete remission can be expected in about 80% of the patients (6–8). The relapse rate of 5% in this series may be artificially low due to the small numbers involved. No relationship between initial platelet count and relapse could be ascertained. No relationship was found between initial onset of disease and timing of splenectomy as related to platelet response. This finding is in keeping with the report by DiFino et al (9). Also, no correlation was identified between postoperative in-hospital platelets counts following splenectomy and subsequent relapse. It is clear, however, that splenectomy does yield better results than steroids in the treatment of refractory cases of this disease. It is also clear that this can be accomplished with acceptable morbidity and mortality rates.

All patients in this study received prednisone preoperatively and all received intravenous steroid perioperatively. No relationship was demonstrated between the preoperative dosage of prednisone and postoperative platelet counts.

Serious infections were common in the late postoperative follow-up (7%). This finding is consistent with other reports of infectious complications following splenectomy for hematologic diseases. It is of interest that only partial- and nonresponders developed infectious complications in this series. Perhaps they had a different form of the disease making them more susceptible to infectious problems. This study clearly points to the necessity for vaccination against pneumococcal bacteria and the need for massive antibiotic therapy in splenectomized patients who develop respiratory infection or other infectious diseases.

All of the partial- and non-responders, as well as the patients who relapsed, had Howell-Jolly bodies in their peripheral blood smears. However, DiFino et al (9) have shown that this does not exclude viable splenic tissue. Therefore, attempts to identify and locate accessory splenic tissue should be pursued, as reoperation with removal of accessory splenic tissue has been successful in treating relapses. In this series, repeat liver-spleen scans did not reveal any patient with an accessory spleen.

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Harlequin Fetus in Twins

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Abstract

A case of a harlequin fetus in dizygotic twins is reported. The harlequin fetus is the severest expression of nonbullous congenital ichthyosiform erythroderma, an autosomal recessive disorder. Prenatal diagnosis is possible with fetoscopy and fetal skin biopsy.

The term ichthyosis refers to the visual appearance of a heterogenous group of patients who develop platelike scales on their skin surface. These disorders are distinguished by their inheritance patterns, clinical picture, and histologic features (1–3).

The harlequin fetus is an autosomally recessive form of congenital ichthyosiform erythroderma in its severest expression (1, 2). The first reported case of a harlequin fetus in the United States dates from 1750 (4). We report here the unusual case of a harlequin fetus in dyzygotic twins.

Case Report. A 35-year-old Dominican woman, Para 1001, registered at the City Hospital Center at Elmhurst on Long Island, NY, during the midtrimester. The father was a 38-year-old Dominican, a first cousin of the mother. There was no history of medication use or drug or alcohol abuse and no family history of skin disorders. She had delivered vaginally a normal, full-term male infant, weighing 5 lb 8 oz, in 1974. She was referred for genetic counseling and amniocentesis, but she refused. On the second prenatal visit, uterine size was noted to be greater than gestational age. A sonogram showed a twin gestation with both biparietal diameters consistent with 32 weeks of pregnancy. Mild polyhydraminos was present, with no anomalies noted. The pregnancy was complicated by Class A diabetes controlled by diet; all weekly two-hour postprandial tests of blood sugars were normal. At 38 weeks she was at full dilation in active labor. Twin A, a vertex male infant, was delivered vaginally, with apgar scores 8, 9 and a birth weight of 2,000 gm. Twin B, a breech female infant, was delivered vaginally with a birth weight of 2,140 gm and apgar scores of 6, 7. Twin B was grossly dysmorphic (Fig. 1).

The affected infant's entire body was covered by whitish-yellow thick scales and deep fissures, replacing all normal skin. The eyes were small slits with marked ectropia. The ears were rudimentary. The mouth was held open in an O shape with ectropia of the lips. The infant survived 11 days and died of sepsis. At postpartum, skin showed extensive hyperkeratosis and parakeratosis with absence of the granular layer (Fig. 2). Immunofluorescent studies revealed increased amounts of prekeratin in the parakeratotic layer.

Discussion. Ichthyosis is a group of heterogeneous, heritable disorders characterized by a thickened skin that leads to cutaneous scaling. The most useful classification is that proposed by Wells and Kerr, who classified the various types based on inheritance patterns (1).

The harlequin fetus is considered the severest expression of nonbullous congenital ichthyosiform erythroderma (1, 2), which is autosomally recessive. These infants are often premature, of low birth weight, and usually die shortly after birth (2). However, a case of an infant surviving nine months has been reported (5). Death is usually due to sepsis, pneumonia, mechanical restriction of respiration, inspissation of plaquelike material in utero, electrolyte imbalance, or dehydration secondary to abnormal skin fluid losses (2, 5).

The histologic characteristics are generalized hyperkeratosis, parakeratosis, and an increase in the granular layer, uniformly distributed over the trunk, limbs, and face (2, 3).

The precise abnormality in the epidermis is

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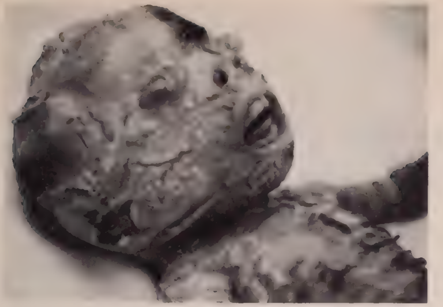

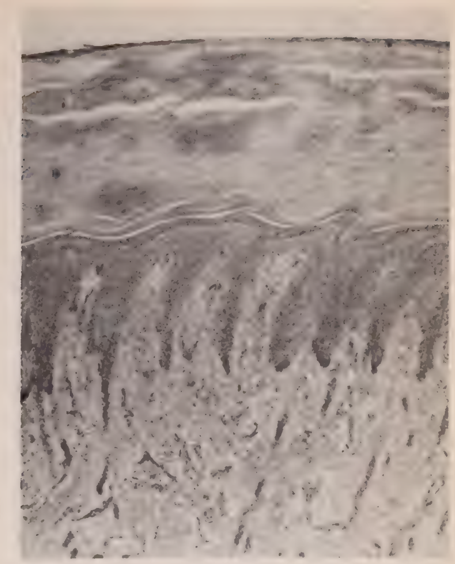

FIG. 1. **Left** Face of affected fetus.
FIG. 2. **Right** Hyperkeratosis and parakeratosis of skin of harlequin fetus; absence of granular layer.

still unknown. Craig, using x-ray diffraction studies on the stratum corneum, revealed the presence of a poorly oriented cross-β fibrous protein, rather than the usual ∝-protein (6). This was confirmed by Baden, who was able to demonstrate an abnormal amino acid composition in the stratum corneum. The higher value for proline and the lower value for glycine were most striking (7). Buxman was unable to confirm these changes, but did demonstrate an elevated level of cholesterol and triglycerides in the stratum corneum (5).

The literature reports more than 100 cases of harlequin fetus, in individuals of all races, with no instances of afflicted members in successive generations; there are equal numbers of afflicted males and females. These findings, together with a high frequency of parental consanguinity, suggest the condition results from homozygosity for a rare autosomal recessive gene (3).

In families at risk, prenatal diagnosis may be made by fetoscopy. In 1968, Elias was able to obtain a skin biopsy of a 20-week fetus. Histology showed a keratin layer thicker than expected for the gestational age of the fetus. The premature hyperkeratosis was most marked around hair follicles and sweat ducts. Skin samples obtained from control fetuses at a comparable gestational age showed an epidermis consisting of squamous epithelium, only a few cells in depth, with minimal keratinization. Amniotic fluid cytology was not helpful in diagnosis (8).

In summary, the harlequin fetus is an autosomally recessive disorder causing generalized hyperkeratosis. The exact consistency of the abnormal stratum corneum is not known, but abnormalities in protein content, cholesterol, and triglycerides have been found. Prenatal diagnosis is possible with fetoscopy and fetal skin biopsy.

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Veno-Occlusive Syndrome of the Liver in an Alcoholic Man

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Abstract

Veno-occlusive syndrome of the liver has been associated with the drinking of "bush" teas made from *Senecio* and *Crotalaria* species and containing pyrrolizidine alkaloids. The disease has also been linked to other etiologic factors, such as radiation and toxic injury. We studied a typical case of veno-occlusive syndrome occurring in association with alcohol abuse and in the absence of all other known causes.

In addition to bush tea, several other factors have been implicated in the pathogenesis of veno-occlusive syndrome. These include bone marrow transplantation (1–3), chemotherapy (1, 4, 5), radiation (2, 6), aflatoxin, and dimethylnitrosamine (7). Increasingly, alcohol abuse is being recognized in association with veno-occlusive syndrome. Goodman and Ishak recently demonstrated the importance of occlusive venous lesions in causing portal hypertension during the precirrhotic stage in alcoholic liver disease (8). Scott et al (9) have suggested that this entity should not be called veno-occlusive disease (VOD), but rather a veno-occlusive syndrome (VOS). We recently had the opportunity to study a case of VOS associated with alcohol abuse.

Case Report

A 30-year-old white man was admitted to the Veterans Administration Medical Center, Bronx, N.Y., after suffering for one month from scleral icterus, abdominal fullness, nausea, and right upper quadrant pain. He had been a heavy drinker for several years, but had been well. He had undergone no previous surgery or biopsies and was not taking any medication. It is not known if he was drinking to excess at the time of admission.

In addition to the marked icterus, he had an enlarged, tender liver whose edge was palpable 15 cm below the right costal margin, marked abdominal distension with fluid waves, palmar erythema with numerous ecchymoses and petechiae over all extremities, and spider angiomas on the anterior chest and abdomen. The remainder of the physical examination was unremarkable.

Blood tests yielded the following results. The hemoglobin value was 11.6 g/100ml, the leukocyte count was 26,900/mm^3 with 13% bands, 76% neutrophils, and 11% lymphocytes. Platelets numbered 137,000/mm^3. The sodium value was 123 mEq/l, potassium 2.9 mEq/l, chlorides 68 mEq/l, CO_2 32 mEq/l, blood urea nitrogen 68 mg/100 ml, glucose 82 mg/100 ml, total protein 7.4 gm/100, albumin 2.2 gm/100 ml, uric acid 15.9 mg/100 ml, total bilirubin 19.3 mg/100 ml, calcium 8.1 mg/100 ml, phosphorus 6.3 mg/100 ml, creatinine 5.0 mg/100 ml, lactic dehydrogenase (LDH) 300 U/L, glutamate pyruvate transaminase (GPT) 22 U/L, glutamate oxaloacetic transaminase (GOT) 267 U/L, gamma-glutamyl transpeptidase (GGT) 324 U/L, alkaline phosphatase 272 U/L, amylase 133 S. units, prothrombin time 17.3/11.6 sec.

Hepatitis B surface antigen (determined by radioimmunoassay) was not demonstrable. Electrocardiogram and chest X-ray were unremarkable.

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The admitting diagnosis was alcoholic hepatitis and renal failure due to hepatorenal syndrome. The patient was hydrated and given thiamine, vitamin K, and potassium chloride, and he was treated with ampicillin, clindamycin, and gentamycin. A Scribner shunt was inserted for renal dialysis one week after admission because of worsening renal failure. He had hematemesis and passed clotted blood rectally. Fibrin split products were detected in the serum. The platelet count dropped to 54,000/mm^3; the prothrombin time was now 25.6/15.8 sec, partial thromboplastin time 96.6/49.0 sec, and thrombin time 38.5/17.4 sec. He was thought to have disseminated intravascular coagulation (DIC). A pericardial friction rub was noted and he had visual hallucinations and became disoriented with respect to time, place, and person. *Pseudomonas aeruginosa* was cultured from blood. He died on the twenty-second day in hospital.

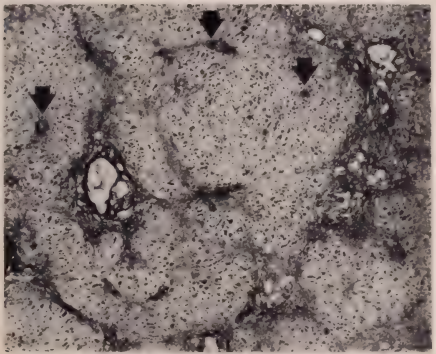
Necropsy Findings. Postmortem examination discovered a hemopericardium (400 cc) and pericarditis with left fibrinous pleuritis and bilateral pleural effusions. Two liters of orange ascitic fluid were present. The liver weighed 1,640 gm. The hepatic parenchyma was soft, greasy, and yellow-red. Microscopically, there was central vein sclerosis with marked intimal proliferation and partial occlusion by loose connective tissue. Branches of portal veins also showed similar occlusive changes (Figs. 1, 2). Multiple bile plugs and pools were present. The portal tracts contained a minimal, mixed inflammatory infiltrate with minimal bile ductular proliferation. Marked fibrosis was seen around individual hepatocytes. Up to 6 sections of the liver were examined from different areas.

Diffuse septal fibrosis, with transition to cirrhosis, was also present, in addition to mild focal steatosis and pronounced autolytic change. Marked portal fibrosis was seen with porto-central bridging. The spleen was enlarged and weighed 340 gms; it was congested microscopically. No esophageal varices were identified. Pancreatitis was not seen. Thrombi were not found in any organs.

Other findings included bilateral pulmonary edema and hemorrhage, and renal edema with bile plugs in the medullary tubules. In addition, there was a purulent meningitis.

Discussion

Veno-occlusive disease of the liver (VOD) was originally described in Jamaicans using bush teas made from *Senecio* and *Crotalaria* species for medicinal purposes (10–12). These contained pyrrolizidine alkaloids. VOD may have acute, subacute, and chronic stages (7). The acute stage is marked by sudden ascites with painful hepatomegaly. The condition has been described in patients of all ages but occurs most often in infants between the ages of 18 months and 3 years. Many patients recover within 4–6 weeks; some die of liver failure, and others progress to the subacute phase. There is firm hepatomegaly and recurrent



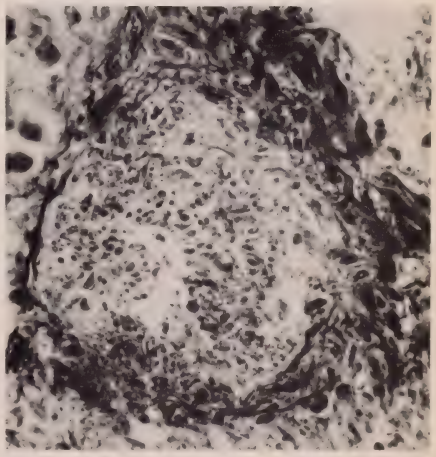


FIG. 1. **Left** Photomicrograph of liver showing (arrows) three obliterated central veins (elastic van Gieson stain, ×100, slightly reduced).

FIG. 2. **Right** High-magnification photomicrograph of central vein showing occlusive loose connective tissue proliferation, and minimal sclerosis, of intima (elastic van Gieson stain, ×400, slightly reduced).

ascites. Patients presenting in the stage of chronic VOD may be clinically indistinguishable from those having other forms of cirrhosis. Thirty percent of 77 cirrhotic Jamaicans classified as having nonportal cirrhosis were shown to have VOD (13).

Luminal obstruction of the centrilobular and sublobular hepatic veins by loose connective tissue is the hallmark of VOD (7). Larger veins are unaffected. The perivenular hepatic parenchyma may become necrotic, with subsequent fibrosis.

It has been postulated that the obliterative lesions result from an interruption of the blood flow (14). In vivo studies of rat liver 10–16 hours after the administration of the alkaloid fulvine, prepared from Jamaican *Crotalaria fulva* plants, showed that much of the sinusoidal blood supply was unable to perfuse the central veins because of thrombosis of the sinusoids close to the terminal hepatic venules (15).

VOD may also be induced by dimethylnitrosamine and aflatoxin (7). In addition, it has been reported in a patient receiving azathioprine after a renal transplant (4), in patients who have had chemotherapy for acute leukemia (5), and in patients undergoing immunosuppressive therapy associated with bone marrow transplantation (1, 3).

The central hepatic vein is also characteristically altered in alcoholic hepatitis (16). This typical lesion of alcohol-induced central vein sclerosis lacks the obliterative luminal proliferation of loose connective tissue which characterizes VOD, a feature which was present in our case. Portal hypertension may precede the development of cirrhosis in alcoholics. In our case, the liver was in a stage of developing cirrhosis, with portal hypertension expressed as ascites and splenomegaly. Unlike the alcoholic veno-occlusive lesions, which appear before cirrhosis, the veno-occlusive lesions due to other etiologic agents are seldom seen in the absence of cirrhosis (8). Therefore, it may be that veno-occlusive lesions combined with phlebosclerosis contribute to the portal hypertension in the absence of cirrhosis. Another point of interest is that Ishak et al (8) mention a nodular, shrunken, atrophic liver in conjunction with veno-occlusive lesions. This finding was not encountered in our case, since the 1640 gm liver was neither nodular grossly nor was it shrunken.

In conclusion, veno-occlusive disease can be observed in alcoholics and may be a useful clue to predict those patients likely to develop signs of portal hypertension in the absence of cirrhosis. In order to evaluate this, stain for elastic tissues should be performed in all liver biopsies from alcoholic patients.

Acknowledgments

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Purulent Pericarditis Caused by *Streptococcus anginosus-constellatus*

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Introduction. The viridans streptococci are generally considered to be a homogeneous group of alpha-hemolytic bacteria with low pathogenicity except in the case of subacute bacterial endocarditis. Certain species have, in fact, been isolated in a variety of purulent diseases. One such species, *Streptococcus anginosus-constellatus,* has been reported to cause pyogenic abdominal, pulmonary and intracranial infections (1). This report details a case of purulent pericarditis caused by *S. anginosus-constellatus* and indicates the need for detailed identification of viridans streptococci in appropriate clinical situations.

Case Report. The patient, a seventeen-year-old girl, was well until July 29, 1981, when she developed a sore throat, midsternal chest pain, and dyspnea. She was initially treated with erythromycin for pharyngitis. The following day her symptoms had progressed, and she was admitted to a community hospital. On admission the patient was in moderate distress. Her temperature was 38.3°C; heart rate 130 per min.; blood pressure 132/70. The pulses were full and equal. The lung fields were clear to auscultation. The abdomen was benign. Auscultation of the heart revealed a rapid, regular rhythm. Heart tones were normal. No cardiac murmurs or rubs were appreciated. A chest x-ray revealed an enlarged cardiac shadow with clear lung fields. A large pericardial effusion was detected by M-mode echocardiography. The hematocrit was 40.4%; white blood cell count 15,300 (poly 27%, band 56%, lymph 14%, mono 2%, eosin 1%).

The presumed diagnosis was viral pericarditis with pericardial effusion.

The patient lived in a semirural area outside New York City. There was no history of significant illnesses or of congenital or acquired cardiovascular defects. All family members had been well prior to admission. However, four weeks prior to the onset of illness, a pet hamster and parakeet died for unknown reasons.

Indomethacin and then prednisone therapy was begun. Blood cultures obtained upon admission and during hospitalization were sterile. The ASLO titer was less than 200 T.U.; mono spot test for infectious mononucleosis, negative; PPD, negative; Ebstein-Barr virus titers yielded no evidence of recent infection. By the ninth hospital day the patient was in manifest cardiac tamponade with an 18-20 mmHg paradoxical pulse. Pericardiocentesis yielded 1,000 cc of purulent material. Gram stain of the fluid showed gram-positive cocci in chains. Cultures revealed pure growth of alpha-hemolytic *Streptococcus anginosus-constellatus,* with the following reactions: esculin +, lactose −, glucose +, maltose +, mannitol −, sucrose +. The organism was sensitive to penicillin, cephalothin, erythromycin, chloramphenicol, clindamycin, and sulfonamide when tested using Kirby-Bauer discs. No mycobacteria, fungi, or anaerobic organisms were isolated. Because the patient was allergic to penicillin, therapy with intravenous cefazolin sodium, 8 gm per 24 hours, was initiated.

In the subsequent days, the patient developed bilateral pleural effusions and evidence of cardiac constriction. The patient was transferred to The Mount Sinai Medical Center for pericardiectomy.

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At surgery, the anterior parietal pericardium was thickened and fibrotic. A thick purulent exudate was found in the pericardial space. The anterior visceral pericardium was constrictive and was, therefore, resected. Eight hundred cc of purulent material was drained from each pleural cavity. Gram stain of both pericardial exudate and pleural fluid showed gram-positive cocci in pairs. Wet mount, acid-fast, and Giemsa smears showed no other pathogens. Cultures failed to grow bacteria, mycobacteria, fungi, or viruses. However, the patient had received several doses of the antibiotic prior to surgery.

Following the operation and a long course of cefazolin therapy, the patient made complete recovery. Acute and convalescent antibody titers for coxsackie B_{1-5}, LGV (for *Chlamydia*), adenovirus, rubella, cytomegalovirus, herpes, and Ebstein-Barr viruses failed to demonstrate a significant rise or fall. Antibody against *Proteus* OX-K, OX-2, and OX-19 showed no rise in titer in serial specimens. A complement fixation test failed to detect antibody to rickettsia or *C. psittaci*. Serum immunoglobulins, complement components, and T-lymphocyte functions were normal. Evidence of underlying neoplastic, collagen-vascular, pulmonary, or cardiac disease was sought; no abnormalities were found.

Discussion. *Streptococcus anginosus-constellatus* is normally found in both the oral cavity (gums, pharynx) and the intestine. This organism may invade the host from these sites. To our knowledge, purulent pericarditis caused by *S. anginosus-constellatus* has not been previously described; however, speciation of viridans streptococci was not commonly performed in the past. Indeed, pericarditis due to any viridans streptococci is unusual (2), and such cases have resulted from contiguous—not hematogenous—spread. In our patient it would appear that pericarditis resulted from hematogenous spread from the oropharynx. Blood cultures were repeatedly negative; however, the patient had received erythromycin prior to taking blood for culture. The empyema, which followed the development of pericarditis by several days, was likely secondary to extension of pericardial infection to the pleural space. It is possible that the patient first developed a nonbacterial pericardial effusion which became superinfected during an episode of bacteremia. Against this possibility was the lack of serologic or culture evidence of infection with such agents.

Streptococcal isolates are usually designated *S. viridans* if they are alpha-hemolytic on blood agar and they are not pneumococci or enterococci. Traditionally, further identification of viridans streptococci has been based on Lancefield typing and colony morphology. However, numerous viridans streptococci are not typeable using Lancefield antisera (3). Isolates found to be similar in hemolysis pattern and serologic typing can demonstrate markedly differing metabolic and physiologic characteristics; conversely, strains dissimilar in culture characteristics and Lancefield type may show identical metabolic properties. Two classifications of viridans streptococci based primarily on physiologic reactions of the organisms have recently gained acceptance. Facklam (3) separated viridans streptococci into ten species, of which *S. anginosus-constellatus* is one. Coleman and Williams (4) divided viridans streptococci into pneumococci and five other species (*S. salivarius, S. mitior, S. milleri, S. sanguis, S. mutans*). Most strains designated *S. milleri* by Coleman and Williams (4) can be divided into one group which forms acid from lactose (*S. MG-intermedius*) and another which does not (*S. anginosus-constellatus*) (3). Streptococci identified as *S. anginosus-constellatus* (or *S. milleri*) have been isolated, often as the sole isolate, from inflamed appendices and maxillary sinuses, intraabdominal, pelvic, hepatic, and intracranial abscesses, and from patients with cholangitis, empyema and endocarditis (5–7).

This report and those of others noted above clearly show that viridans streptococci can cause a variety of purulent diseases. Detailed identification of a *Streptococcus viridans* strain isolated from clinical material may provide helpful information about the source and significance of a presumed offending organism.

AUTHOR'S NOTE: Since acceptance of this manuscript, a case report of purulent pericarditis following myocardial infarction due to *S. MG-intermedius* has been published (Hauser AM et al. Myocardial infarction and purulent pericarditis. Cardiovasc Rev Reports 1983; 4:971–974).

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An Association of Parotid Carcinoma with Von Hippel-Lindau Syndrome

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Abstract

Von Hippel-Lindau syndrome is the association of central nervous system hemangioblastomas with other lesions of benign or grave clinical significance. Most patients manifest only a few of the many documented abnormalities at different times in their clinical course. A patient is discussed here in whom parotid carcinoma was discovered two years prior to the diagnosis of Von Hippel-Lindau syndrome. Because of the rarity of parotid carcinoma and the malignant tendency of the renal cysts of Von Hippel-Lindau syndrome, it is proposed that parotid carcinoma is another manifestation of this syndrome.

Von Hippel-Lindau syndrome is a genetic disorder characterized both by lesions causing significant mortality and morbidity and by other lesions of generally lesser clinical importance. In 1976, Horton, Wong, and Eldridge collected data on 50 patients from nine families with the syndrome, and drew up a list of 31 lesions among them, diagnosed on the basis of clinical and autopsy findings (1). Of the 31 abnormalities, 25% occurred only once among these patients. Of the many manifestations, hemangioblastomas of the central nervous system and spinal cord, renal carcinoma, adrenal pheochromocytoma, and retinal angioma are of greatest clinical importance (1, 2). Cysts, adenomas, and angiomata of the lung, bone, liver, spleen, pancreas, kidney, ovary, and epididymis are generally found during the search for related lesions. These manifestations also can become clinical problems because they expand or affect endocrine function, as do cerebellar cysts and pancreatic adenomas (3, 4). Ten to twenty percent of patients with the syndrome demonstrate polycythemia, which is thought to be associated with the secretion of erythropoietin by the hemangioblastoma (3, 5, 6).

Most patients do not manifest more than two or three different lesions, and these are usually not all present or of fully developed clinical significance at the time of initial diagnosis (1, 5, 7). The diagnosis is made when a cerebellar hemangioblastoma (Lindau tumor) is found in combination with one or more neoplasms in the central nervous system or elsewhere in the body (8). The syndrome is inherited as an autosomal dominant gene of variable penetrance (1, 2) manifesting itself in 10%–50% of the members of an affected family (7, 9, 10). Thus, a positive family history is not an absolute criterion for diagnosis. The syndrome is usually identified in young or middle-aged adults, but may become manifest for the first time in old age (1, 7).

Case Report. A 71-year-old white man was admitted to The Mount Sinai Hospital in New York for treatment of a space-occupying lesion of the cerebellum. He had been well until two weeks prior to admission, when he experienced several hours of vomiting, for which he was admitted to another hospital. There, he was found to have mild ataxia and a positive Rhomberg sign. A CT scan of the head revealed a large multilobular mass in the left cerebellar hemisphere with supraventricular hydrocephalus. The patient was then transferred to Mount Sinai. Physical examination revealed mild hypertension, ataxia with falling to the left, and a mild left facial weakness. The roentgenogram of the chest, electrocardiogram, and laboratory results were normal except for persistent polycythemia. The patient had never smoked or drunk alcohol to excess. He had a med-

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ical history of mild hypertension for many years, controlled with a small dose of metaprolol tartrate (Lopressor).

Two years prior to admission, the patient had been hospitalized at The Mount Sinai Hospital for a right parapharyngeal mass. This proved to be a malignant adenocarcinoma of the right parotid gland; it was found to be invading the mesenteric muscle, there was no other evidence of spread. The mass was surgically excised and the patient had no further treatment or problems on follow-up examinations. Also on that admission, the patient had difficulty voiding. An intravenous pyelogram showed a large bladder and possible renal cysts. Prostatectomy revealed that the prostate was benign.

The patient had no family history of central nervous system or spinal cord tumors, pheochromocytoma, stroke, myocardial infarction, renal carcinoma, or retinal lesions. His children were alive and without medical problems.

In view of this history, a renal sonogram and CT scan of the body were done. One moderately large, simple cyst was found in each kidney. There were no abnormalities seen elsewhere in the body. A CT scan of the right parapharyngeal region demonstrated no recurrence of the earlier tumor. Tests of his urine for metanephrines and vanillylmandelic acid were normal. The patient underwent surgery, and a large cerebellar hemangioblastoma was completely excised. His hemogram was now normal and remained so for the rest of his hospitalization. His subsequent course was uncomplicated, and he was discharged to be followed by his private physician.

Comments. We believe that this case meets the criteria for Von Hippel-Lindau syndrome on the basis of the combined diagnoses of cerebellar hemangioblastoma, polycythemia, and renal cysts. We also suggest that the parotid carcinoma was associated with this syndrome.

The abnormalities seen with Von Hippel-Lindau syndrome are of ectodermal (pheochromocytoma), mesodermal (visceral neoplasms), and endodermal (angiomata) origin, so that the ectodermal origin of the parotid gland is interesting but not useful as part of the criteria for diagnosis.

Although neoplasms of the parotid are not rare, they are not often malignant (11, 12). Cancer of this gland makes up only about 1% of all malignant neoplasms. There has been much controversy over the histologic classification of parotid cancer and its usefulness with respect to treatment and prognosis (12, 13). However, it is well established that invasion characterizes malignant rather than benign parotid neoplasms and that parotid carcinoma is rare (12, 13). It is also known that the renal cysts seen in Von Hippel-Lindau syndrome undergo malignant transformation much more frequently than isolated renal cysts or those of polycystic kidney disease (2, 5, 8, 14). It is therefore reasonable to postulate that parotid malignancies would occur with greater frequency when associated with Von Hippel-Lindau syndrome.

In view of this evidence and the fact that many lesions associated with Von Hippel-Lindau syndrome have been documented only once, the occurrence of both parotid carcinoma and Von Hippel-Lindau syndrome in this patient seems more than fortuitous. We suggest that, in future, a thorough search of the parotid glands in patients with Von Hippel-Lindau syndrome may produce similar cases.

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Breast Cancer: Risk Factors and Etiology

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The cost of breast cancer to society is enormous in terms of both mortality and morbidity. In the U.S. alone, it accounts for roughly 34,000 deaths every year, and will affect one in every 11 women alive today (1). In spite of new approaches to treatment and new means of early diagnosis, such as mammography, death rates from breast cancer have not changed significantly in the past 50 years (1, 2). Though continued high death rates primarily reflect the limitations of treatment methods, they also indicate failure of early detection. Most breast cancers are discovered as palpable breast lumps, and usually are found to have associated lymph node metastases at the time of surgery (2). Obviously, detection before the cancer has spread to the lymph nodes would improve survival.

At present, the most sensitive method available for breast cancer detection is mammography. Preliminary results from mass screening programs using mammography show a reduction in fatality rates among screened populations when compared to controls, the reduction being most evident in women 50 years old or older (3, 4). However, though mammography can detect nonpalpable cancers less than 1 cm in diameter, it also delivers a dosage of radiation which can increase neoplastic transformation (5). Therefore, the present recommendations of the American College of Radiology advise yearly mammograms in asymptomatic women over 50 and, among women younger than 50, only for those classified as "high risk."

There are problems, however, with risk classification. In spite of numerous attempts at defining risk parameters, no group of factors can be found that will account for most cases of breast cancer. Thus, concentration on women currently known to be at high risk would still miss a large number of cases. Conversely, there is a point where radiation exposure from mass unselected mammographic screening would create more cancers than it would prevent (6). Thus, the problem remains of adequately defining a high-risk group. Ideally, members of such a group could be distinguished from the population at large by means of history or a simple biochemical test. Definition of risk factors for breast cancer is made difficult by the heterogeneity of the disease. There are several histological types of breast cancer. Breast neoplasms differ in the presence or absence of estrogen receptors, the absence being correlated with a poorer prognosis. In addition, premenopausal disease has different characteristics from postmenopausal disease (7). Thus, one is dealing with a variety of entities which have one common feature, malignancy, but different behaviors and etiologies. These problems have understandably led to intensive epidemiologic study of this group of disorders (5, 8, 9). The ensuing discussion briefly reviews current medical knowledge obtained from this research.

Risk Factors

Sex. The single most important risk factor is clearly sex. Though breast cancer is not exclusively a disease of females, males are affected at only one hundredth the rate of females. Males with Klinefelter's syndrome (XXY) have an incidence of breast cancer 20 times higher than that of normal males (10, 11). Whether the increase is related directly to endocrine status or to the gynecomastia often associated with this syndrome is unknown. It is possible that the increase in breast tissue results in the presence of a larger number of cells susceptible to neoplastic change.

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Age. The incidence of breast cancer increases with age up until middle age. In countries with high prevalence of the disease, incidence continues to increase after middle age, while in countries with low prevalence, a plateau is reached at middle age and incidence may remain stable or decrease thereafter (8, 12). Considering the latency period of about 15 years for development of cancer, the variation between countries observed in postmenopausal cancer incidence may well be due to differences occurring in premenopausal life. The fact that the incidence of premenopausal breast cancer does not vary greatly with geography, while great differences between countries are found in postmenopausal cancer incidence, suggests different etiologies for premenopausal and postmenopausal disease. Premenopausal cancer has greater familial aggregation and is more often bilateral. This finding indicates an inherent increased susceptibility to neoplasia in the premenopausal group.

Geography. The incidence of breast cancer, especially the postmenopausal type, varies greatly worldwide, from approximately 85 per 100,000 among affluent whites in Western industrialized countries to 11–13 per 100,000 in Japan and Muslim countries (12, 13). Offspring of Japanese migrants to high-risk areas manifest higher rates than their counterparts in Japan. Several different hypotheses have been proposed to explain the geographic differences: diet, differences in reproductive patterns and thus in endocrine status, genetic differences, and differential exposure to unknown environmental factors (8, 12, 13, 14). Clearly, increased rates among migrants to high-risk areas indicates that environment has a significant etiologic influence.

Family History. First-degree relatives of women with breast cancer have breast cancer rates two to three times that of the general population. The risk increases further if the disease is bilateral or premenopausal (8, 12, 14, 15). Clusters of families have been described with extremely high rates (16). Though familial clustering suggests a genetic factor, exposure to a common environmental factor has not been ruled out.

Reproductive Experience. *Parity:* Risk of breast cancer is increased in women who have their first child after age 30. Women having their first child before age 18 have one third the risk of those who delay childbirth until age 35. Only full-term pregnancy is protective, and parity beyond the first pregnancy does not appear to make a difference in most populations studied (12, 14, 17).

Lactation: The belief that lactation protects against breast cancer has not been confirmed by recent epidemiological studies. When parity is held constant, no differences can be seen in lactation experience between breast cancer cases and control groups (12).

Oophorectomy: Surgical menopause is associated with a 40% reduction in breast cancer risk, the greatest reduction being in women undergoing oophorectomy before age 35. The protective effects of early oophorectomy extend for at least thirty years, women who have had early oophorectomy having decreased rates of breast cancer at all ages after surgical menopause. Most of these studies have evaluated women receiving no estrogen replacement after surgery (8, 12).

The hypothesis that ovarian activity plays a role in the etiology of breast cancer is supported by studies on ovariectomized dogs. The risk of breast cancer in female dogs can be shown to be directly related to the number of estrous cycles experienced before surgery. The risk in dogs spayed before the first reproductive cycle is 1% the risk of intact animals (12). In women, the number of menstrual cycles experienced may be positively correlated with breast cancer risk. Case control studies have shown a small increase in risk of developing breast cancer in women having early menarche. Similarly, some investigations have shown that women entering menopause after age 55 have twice the risk of those with natural menopause before age 45 (8, 12, 15). These relationships are evident in spite of the fact that women with early menarche and late menopause might be expected to achieve greater parity and thus to benefit from the protective effects of early pregnancy.

Previous Benign Breast Disease. Women with a history of benign breast disease have a two- to three-fold increased risk of developing malignant disease. The increase is not the same with all types of benign breast disease; epithelial hyperplasia is associated with the highest increase in risk: four- to seven-fold (8). It is unclear whether patients with epithelial hyperplasia and women with breast cancer have the same distribution of risk factors. In spite of their increased risk, women with benign breast disease make up only 5% of cases of breast cancer (8, 12). However, some studies report coexisting benign lesions in 39% of breast cancer cases (12). It is not known whether benign lesions progress to become malignant or whether benign and malignant lesions have similar etiologies and are thus more likely to coexist.

Radiation. A linear relationship can be demonstrated between radiation dose and incidence of breast cancer, especially among women younger than 20 at the time of exposure. The evidence comes from women undergoing multiple fluoroscopies or radiation therapy, and from atomic bomb survivors. The latency period between exposure and development of cancer is about 15 years. In all cases studied, dosages have been high, 50 rads or more (5, 12). As with other radiation-induced cancers, the nature of the dose-response relationship at very low levels is unknown.

Diet. The higher rates of breast cancer in Western countries have led to the speculation that dietary factors, especially fat consumption, play a role in the genesis of breast cancer. However, it has been difficult to demonstrate a direct association. Dietary fat could influence breast cancer development by lowering the age of menarche or altering steroid metabolism. A few controlled studies have shown increased beef and pork consumption associated with an increase in breast-cancer cases as compared with the incidence among controls.

Etiology

From all available data (animal experiments, tissue culture, and epidemiology) three major hypotheses of breast cancer etiology have emerged: viral, genetic, and endocrine.

Viral Hypothesis. Evidence for the viral hypothesis comes mostly from laboratory studies on intact animals and from tissue culture. A virus causing mammary tumors in mice has been identified (MMTV). It has been shown that oncogenesis by MMTV is indirect and probably involves activation of endogenous cellular transforming genes. Attempts to identify a similar virus in humans have been unsuccessful (9). However, it has recently been shown that DNAs isolated from MMTV-induced tumors and from a human breast-cancer line are both able to transform mouse 3T3 cells in vitro. Further analysis of transforming DNA's showed that oncogenes from both MMTV-induced tumors and human breast-cancer cell lines had similar patterns of sensitivity to a battery of restriction endonucleases, indicating similarities in their active gene sequences (18). This suggests that in both mouse and human tumors, the gene sequences activated during neoplastic transformation are similar even if the trigger to transformation (MMTV in mice, unknown in humans) is different. It should be pointed out that transformation of 3T3 cells after DNA transfer is only an indirect indicator of the neoplastic state. The inability to identify human mammary-tumor viruses is consistent with epidemiologic data, which provides no evidence for the viral hypothesis (15).

Genetic Hypothesis. Genetic theories of breast cancer etiology have been put forward to explain the increased risk among relatives of women with breast cancer, the concordance of breast cancer in monozygotic vs. dizygotic twins, and the marked difference in rates among different races (12, 16). However, none of the three factors mentioned provides convincing evidence that genetics is a primary cause of breast cancer. Women with a family history of breast cancer account for less than 10% of patients with the disease. Thus, no genetic basis is evident in a majority of cases. In addition, though twin studies show differences in concordance between monozygotic and dizygotic twins, concordance in both instances is small: 0.28 for monozygotic and 0.12 for dizygotic twins (16). Thus, whatever role is played by genetics is small. Increased breast cancer rates among XXY males could be explained by postulating an X-linked factor which predisposes to the disease. However, were such a factor present, it would have to be located on a portion of the X not subject to X-chromosome inactivation, because as in XX females, the supernumerary X of XXY males undergoes virtually a total inactivation.

The relative insignificance of genetics is born out by studies of rates between different races. Migrants from low-rate areas to high-rate areas acquire high rates after one generation. Racial and geographical differences could be explained by differences in risk factors other than race: age at first birth, age at menarche, and so on. However, a difference in genetic susceptibility cannot be ruled out.

Attempts to find an association between specific genetic markers, such as blood group antigens, polymorphic red cell enzymes, serum proteins, or human leukocyte antigens, have so far been unsuccessful (8, 12, 16). The identification of such a marker could provide a way of detecting a susceptible population. For this approach to succeed, a single gene or a small group of genes must be responsible for susceptibility to malignancy and in addition must be in linkage disequilibrium with an identifiable marker such as a blood group antigen.

Endocrine Hypothesis. The fact that women have one hundred times the breast cancer rates of men, that breast cancer occurs almost exclusively after puberty, that early oophorectomy and early pregnancy are protective, and that breast tumors are responsive to hormones, all point to an endocrine etiology of breast cancer. Estrogens are the most seriously implicated hormones, and have been found to be co-carcinogens in rodents (19).

Several mechanisms have been proposed to explain the role of estrogens in breast cancer. One is based on the relative carcinogenic properties of estriol (E3) vs. estrone (E1) and estradiol (E2). E1 and E2 are more potent carcinogens in rodents than E3, and in some studies E3 has been shown to protect rats against breast cancer. In humans, it has been reported that women with breast cancer have lower urinary E3/E1 + E2 ratios than control women, and that Japanese women (low risk) have higher urinary E3/E1 + E2 ratios than Caucasian women (high risk). Thus it has been proposed that estriol competes with the more potent estrogens for binding sites on breast tissue and that higher estriol concentrations protect against breast cancer by preventing the binding of E1 and E2 (19). Additional support for this hypothesis is the fact that urinary E3 levels rise during pregnancy and remain higher in parous women than in nulliparous women (20). Thus the estrogen binding hypothesis could explain both the geographic difference in breast cancer incidence and the protective effects of early pregnancy.

However, this hypothesis assumes that urinary estrogen levels accurately reflect circulating plasma levels and production rates of estrogen metabolites. This assumption is challenged by studies that show circulating E3 levels to be the same in women with high or low E3 excretion (19). Thus the differences observed in urinary levels probably reflect differences in pathways of estrogen disposal. Factors influencing disposal could have something to do with increased risk of breast cancer, but this has yet to be investigated.

Exogenous estrogens have long been suspect as etiologic agents for breast cancer. However no significant association has thus far been found between use of either oral contraceptives or postmenopausal estrogen replacement and development of breast cancer (21, 22).

Another proposed mechanism of estrogen oncogenesis is that prolonged estrogen stimulation in the absence of progesterone predisposes to the development of breast cancer (23). In the normal menstruating woman, progesterone is produced by the corpus luteum in the luteal phase of the menstrual cycle. Progesterone production is thus dependent on ovulation. The "estrogen window" hypothesis predicts that susceptibility to tumor induction will be higher between menarche and the establishment of regular cycles, and in the perimenopausal period (19, 23). These two periods are ones when anovulatory cycles, and thus inadequate progesterone production, are more common. According to proponents of the estrogen-window hypothesis, women with early menarche and late menopause undergo more anovulatory cycles and thus are at increased risk for development of breast cancer. In addition, they predict that the interval between menarche and the establishment of regular cycles will be longer in women who have developed the disease. Recent attempts to confirm these predictions have not succeeded. The interval between menarche and the establishment of regular cycles has been found to be *shorter* in women with breast cancer than in controls. It has also been found that the percentage of anovulatory cycles decreases with years elapsed since menarche, but bears no relationship to age at menarche. In addition, no difference in percentage of anovulatory cycles has been detected between women in high-risk vs. low-risk areas (12).

Thus, while both the estriol hypothesis and the estrogen-window hypothesis are able to explain certain aspects of the epidemiology, neither is entirely consistent with the existing evidence. Moreover, other hormones have also been implicated in breast cancer. Tenuous associations have been noticed between high prolactin levels and malignancy, and between hypothyroidism and breast cancer. A relationship has been found between low excretion of androstenedione metabolites (specifically etiocholanolone) and subsequent development of breast neoplasms. A similarly low excretion has been seen in sisters of patients with cancer. In a prospective study of 4,850 normal women, a sixfold increase in incidence was estimated between women excreting less than 0.4 mg etiocholanolone in 24 hrs over those excreting more than 1 mg. However, these estimates were based on only 27 cases, and other investigators have thus far failed to confirm the findings (19, 20). If this relationship is confirmed by further studies, it could represent an ideal screening method. However, low levels of etiocholanolone excretion are not specific for breast cancer, being found also in association with other malignancies or in association with poor nutritional status (20).

Conclusion

A large number and variety of epidemiologic studies of breast cancer have not succeeded in defining a sufficiently predictive set of risk parameters to allow for effective preventive screening with mammography. Hormonal factors, environmental influences, and perhaps genetic factors have all been correlated to some degree with susceptibility to this disease. The data indicate two strategies for the future. One is continuing study with the goal of better defining the risk parameters, and the other is an effort to develop more effective and less harmful screening procedures. Success with the latter approach is highly desirable, for it allows the physician to test all women regardless of risk assignment. The advantage here is that this disease is so common that even the "low risk" groups are likely to have significant risk and would benefit from screening; the disadvantage is the economic cost of mass screening for any disease.

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Student's Corner *Howard Levin, M.S., Editor*

Postsurgical Adult Respiratory Distress Syndrome: Case Report

MARK A. EPSTEIN, A.B., AND ANTHONY J. STERN, A.B.

Case Report. A 67-year-old white man with an eight-year history of Crohn's disease was admitted to St. Barnabas Hospital, a Mount Sinai affiliate, for elective small-bowel resection. He had been maintained on sulfasalazine, which had kept his intermittent nonbloody diarrhea and abdominal cramps under reasonable control until one month prior to admission. He had become progressively nauseated and anorectic over the past year, and had lost 12 pounds over the last month.

There was no history of diabetes or of cardiovascular, pulmonary, or renal diseases. He had smoked one pack of cigarettes per day for 40 years, but had discontinued use eight years earlier.

On admission, physical examination revealed that the patient was thin and in no distress. The blood pressure was 118/76 mm Hg, and the pulse was 104 per minute and regular. There was no orthostatic change. Respirations were 18 per minute and unlabored. Temperature was 98.8°F. The heart, lungs, and abdomen were normal.

Laboratory studies disclosed hemoglobin of 9.5 gm%, hematocrit of 30.0%, a white blood cell count of $7.5 \times 10^3/\text{mm}^3$, and a platelet count of 705,000. The serum sodium was 140 mEq/liter, potassium 5.0 mEq/liter, chloride 103 mEq/liter, serum carbon dioxide 28 mEq/liter, creatinine 1.1 mg/dl, blood urea nitrogen 13 mg/dl, serum glucose 102 mg/dl, and albumin 2.8 gm/dl. Liver enzymes were all within normal limits. Electrocardiogram and chest x-ray were normal (Fig. 1). The patient was transfused with two units of packed cells on the night prior to surgery.

The patient underwent three small-bowel resections with primary anastomoses and resection of the cecum and appendix. The estimated blood loss was 200–300 cc. He tolerated the procedure well and was given prophylactic cefazolin.

The first postoperative day was uneventful, but in view of his generally weakened state, central hyperalimentation was started via a right subclavian catheter. On Day 2 he developed fever to 102°F. Despite the use of chest physiotherapy, the patient was found to have decreased breath sounds bibasilarly, without rales or rhonchi, and a white blood cell count of $17.8 \times 10^3/\text{mm}^3$, predominantly polymorphonuclear cells. The hemoglobin was stable at 11.7 gm%. Antibiotic treatment was changed from cefazolin to ampicillin and aminoglycoside to provide better coverage. A chest x-ray showed that his lungs were still clear, without infiltrates or effusions. The next day, his temperature rose to 104.1°F. Cultures of blood, urine, and sputum failed to demonstrate a causative agent. Intravenous metronidazole was then added to the regimen. He was placed on a hypothermia blanket in an attempt to control the fever. At no time did he complain of any pain in excess of the usual postoperative discomfort around the incision. His abdomen was nontender and nondistended; his respirations were not visibly restricted by the incisional pain. During the entire hospital course, the wound remained clean, with no signs of infection.

Over the next few days, fever of 102°F and decreased breath sounds bibasilarly with coarse rales at the right base persisted. The white blood cell count had decreased to $7.2 \times 10^3/\text{mm}^3$, but the differential now showed a left shift, with 18% stab forms. Chest x-ray revealed new atelectasis at the right base. The Foley catheter was removed to eliminate a possible source of infection.

The patient's hemoglobin dropped to 8.3 gm%, necessitating transfusion with one unit of packed

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cells; and the serum glucose, which had been previously normal, rose to 385 mg/dl, requiring regular insulin. A chest x-ray taken on Day 6 revealed new patchy densities in the right mid and lower lung fields and at the left base. In view of these new findings, a lung ventilation and perfusion scan was obtained which showed inflammatory changes consistent with pneumonia in the same three lung areas. It was interpreted as having a low probability for being a pulmonary embolus. The abdominal examination continued to be negative: nontender, nondistended, without rebound, rigidity, or guarding. The blood urea nitrogen had risen to 37 mg/dl, however, and the serum creatinine to 3.9 mg/dl. Aminoglycoside treatment was discontinued.

The patient's condition deteriorated over the next three days. He remained febrile to 104°F. Increasing rales and rhonchi could be heard in the right and left mid-lung fields and at the right base. Abdominal examination was benign. Nothing had been cultured from blood, urine, or sputum. He became increasingly weak and intermittently disoriented. Despite the hyperalimentation which had been started postoperatively, the serum albumin fell to 1.9 gm/dl.

In view of the pulmonary findings and persistently negative cultures, fiberoptic bronchoscopy was performed. The findings were nonspecific and included a modest amount of mucopurulent secretions in the right main stem bronchus, but no endobronchial lesions. Gram stain of the secretions demonstrated many white cells, a few gram-positive cocci, and some budding yeasts.

On Day 10 he appeared pale and in a more toxic condition. His temperature was 104°F, his pulse 146/min, and he was markedly tachypneic, with a respiration rate of 42/min. A newly discovered tender liver edge was palpated to 5 cm below the right costal margin, although the entire liver span was only 11 cm. Abdominal ultrasound and CT scans were normal.

His electrocardiogram, which had been normal on admission, now demonstrated first degree arteriovenous (A-V) block. Cultures of the bronchial washings taken at bronchoscopy were positive only for *Serratia marcescens*. Metronidazole was therefore discontinued and the patient was switched to chloramphenicol.

Two days later, he was noticeably weaker and increasingly dyspneic. His chest x-ray showed a pneumonitislike pattern with increased diffuse infiltrates bilaterally and possible congestive heart failure. The patient, now on 5 liters/min of O_2, was transferred to the Intensive Care Unit, where analysis of arterial blood gases showed PO_2 of 69 mm Hg, PCO_2 of 30 mm Hg, pH of 7.42, and a base excess of −4 mEq/liter. He was intubated and placed on a respirator. At this point, his chest x-ray demonstrated a full-blown interstitial pattern consistent with adult respiratory distress syndrome (ARDS).

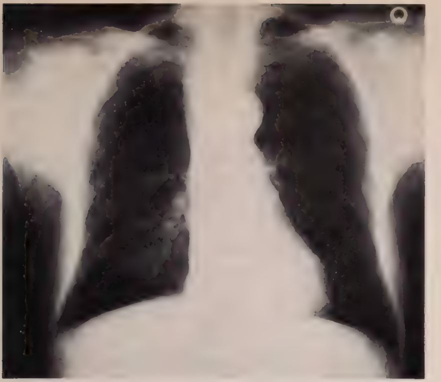
Over the next few days, he became increasingly hypotensive in the range of 90/50 mm Hg. He was given intravenous methylprednisolone and dopamine in an attempt to maintain the blood pressure. A Swan-Ganz catheter was inserted to assess his cardiovascular and pulmonary status more precisely. Results showed pulmonary wedge pressure to be 18 mm Hg, pulmonary artery pressure at 36/18 mm Hg, and right ventricular pressure at 42/6 mm Hg. He continued to have fluctuating blood pressures, and his dopamine requirements increased.

An automated physiologic profile was obtained revealing an average cardiac output of 10.43 l/min, an A-VO_2 difference of 3.4 ml/dl (normal 3.2–5.0), an alveolar arterial O_2 tension difference (with $FIO_2 = 0.85$) of 504.2 mm Hg, and venoarterial admixture (Qs/Qt) of 46.5% (normal 4%–9%). A PEEP of 15 mm Hg was used in an effort to keep the pO_2 above 60 mm Hg. This new data, together with his clinical presentation, was thought to be consistent with a picture of ARDS and secondary shock in a hyperdynamic state.

He continued to deteriorate as multiorgan system failure ensued. He became progressively cyanotic and stuporous, responding only to painful stimuli, with intermittent periods of agitation. His failing renal function required hemodialysis. Arterial blood gas analyses likewise worsened as his pulmonary status slowly collapsed. A chest x-ray on Day 19 (Fig. 2) for the first time showed evidence of congestive heart failure (increased fluid in the interstitium and major fissures, and cephalization of vessels). Furosemide treatment was initiated.

The next day another disturbing series of events occurred. His blood pressure dropped to the range of 90/50 in association with an acute agitated episode. Cardiac measurements revealed pulmonary artery pressure of 42 mm Hg, pulmonary capillary wedge at 15 mm Hg, cardiac output at 7 l/min. With a pressure gradient of 27 mm Hg across the lungs, the cardiac output was thereby less than one third the resistance of the pulmonary circulation. Since this pattern is consistent with an acute pulmonary embolus, a heparin infusion was started.

Over the next four days, fever, respiratory distress, hyperglycemia, liver dysfunction, and finally cardiac arrhythmias developed. Despite



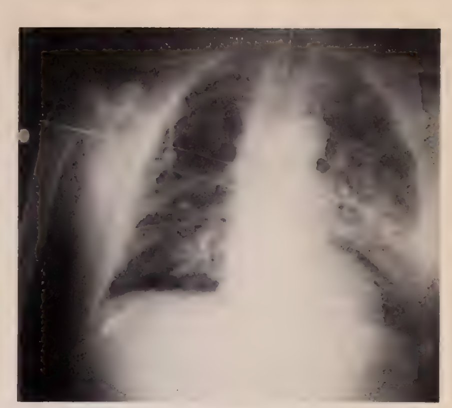


FIG. 1. **Left** Chest x-ray on admission. Mild degree of dextroscoliosis of thoracic spine; lungs free of any infiltrate or consolidation; heart normal in size and configuration.

FIG. 2. **Right** Chest x-ray, Day 19 after surgery. Diffuse bilateral alveolar infiltrate; heart normal in size and configuration; increased fluid in interstitium and major fissures; cephalization of pulmonary vessels. Consistent with ARDS and evidence now of congestive heart failure.

supportive measures, the patient expired on Day 24 after surgery.

Postmortem examination restricted to the chest cavity revealed that the immediate cause of death was respiratory insufficiency. Contributory factors were

- hyaline membranes in alveolae (adult respiratory distress syndrome)
- chronic obstructive pulmonary disease with emphysema, bronchiectasis, squamous metaplasia, and alveolar cell hyperplasia.
- superimposed bronchopneumonia with abscess formation; *Pseudomonas* and *Serratia* by postmortem cultures
- new organizing thromboemboli in large and small branches of pulmonary arterial tree; no source of embolization identified in this limited autopsy
- acute purulent tracheitis
- bilateral serosanguinous pleural effusions, 400 cc on right, 350 cc on left

Discussion. Neither gravely ill nor greatly debilitated upon his arrival for elective surgery, this patient died twenty-six days later, two weeks after the onset of acute noncardiogenic respiratory distress. Of the estimated 150,000 people in the United States afflicted by this condition each year, many are relatively healthy only weeks before the crisis. The mortality is about 50% (1, 2).

Sudden respiratory failure due to nonhydrostatic pulmonary edema has gone by many names since World War I, including "massive collapse of the lung," "traumatic wet lung," "shock lung," "blast lung," and "Da Nang lung." Efforts to describe its pathophysiology and clinical course have been made since the midnineteenth century, especially in association with influenza pandemics and battlefield casualties (3–5). Only in 1967, however, did David G. Ashbaugh, Thomas C. Petty, and their colleagues, calling the process respiratory distress syndrome in adults (ARDS), identify it as an important clinical problem of diverse etiology, thus initiating the wide attention it has received recently (6). Since the late 1960s, the availabilty of advances in bedside testing, particularly arterial blood gas analysis and flow-directed Swan-Ganz catheter measurement of pulmonary capillary wedge pressures, has permitted recognition of ARDS. In addition, shock victims in Vietnam, by frequently succumbing to severe respiratory insufficiency after rapid evacuation and hemodialysis, helped to focus investigative energies on this problem (3, 7).

A preliminary understanding of the pathogenesis of ARDS has evolved in the last few years. In their 1967 *Lancet* paper, Ashbaugh and associates proposed decreased levels of active surfactant as the central cause, for they noted pathophysiologic similarities between adult and infant respiratory distress syndromes (6). Later research has suggested that surfactant abnormalities represent a complication rather than a primary problem. Instead, at present the main culprit appears to be the neutrophil, whose aggregates in pulmonary capillaries liberate superoxide radicals that damage the endothelium, resulting in "leaky capillaries" and hence "permeability edema" (1). These superoxide radicals also destroy structural proteins such as collagen by inactivating α_1-antitrypsin and other pulmonary defense mechanisms against proteolysis. Hence the lung's interstitial architecture becomes especially vulnerable to proteases, also released by neutrophils. Furthermore, these proteases activate complement, leading to increased neutrophil aggregation.

How does this vicious cycle of lung destruction begin? The various clinical precedents of ARDS, including trauma, pneumonia, and septic shock, all trigger the complement cascade. This creates C5a, which attracts neutrophils to the lung, which in turn unload their superoxide radicals and proteases.

In this way a part of the early pathogenic picture can be explained. Additional factors play a role, however, since complement infusions in animals, while promoting lung damage, do not induce the severe interstitial destruction seen in ARDS (1).

Autopsy Findings. In the limited thoracic autopsy performed on this patient, hyaline membranes lining the alveola of both lungs were observed. This, the most characteristic pathologic feature of ARDS, represents the residue of nonhydrostatic edema, whose exudate contains a higher concentration of protein, especially fibrinogen, compared with the transudate of edema secondary to left ventricular failure. The protein content results from the loss of endothelial integrity, allowing transcapillary movement of plasma proteins with molecular radii up to 100 A. The tenacity of the protein-rich exudate prevents rapid lymphatic drainage, and the rise of interstitial osmotic pressure draws further fluid into the interstitium and alveola. The accumulating exudate dissects into the restricted interstitial space and disrupts capillary alveolar junctions, rapidly eliminating the interface for gas exchange (8). The post-mortem evidence of this entire life-threatening process, the wavy pink homogeneous deposits known as hyaline membranes, contain epithelial cell debris, macrophages, fibrin strands, and other plasma proteins (5, 9).

The autopsy report also noted bilateral emphysematous changes, including bronchiectasis, and attributed these to chronic obstructive pulmonary disease. Since ARDS eventually leads not only to pulmonary fibrosis but also to pathologic signs of emphysema (5), the autopsy findings may signify recently introduced abnormalities rather than a chronic subclinical condition. Whether the emphysema constitutes a predisposing cause or a late complication of respiratory failure in this case remains unclear.

The relationship between the ARDS and the bronchopneumonia, abscesses, and gram-negative rods cultured at autopsy is also uncertain. The bilateral pneumonia reported probably represents the original source of sepsis preceding the ARDS, since *Serratia* was cultured from bronchoscopic washings and no intraabdominal abscess could be detected by CT scan or sonogram. Several recent series have found the accuracy of CT scan in localizing abdominal abscess to be consistently above 90%, with a false-negative rate ranging between 1% and 6% (10–12). Nevertheless, it is unfortunate that permission from the family to explore the abdomen at autopsy could not be obtained. Just as pulmonary infection is a common origin of ARDS, it is also a frequent sequela. Even the cultured *Serratia* could have indicated a superimposed process rather than a major etiologic factor. In light of the negative CT scan, however, the lungs are presumed to be the early important site of infection.

Finally, the post-mortem discovery of multiple thromboemboli is of equivocal meaning. Pulmonary thrombi have been observed frequently accompanying cases of ARDS by both angiographic and histologic studies (1). Their significance is disputed. Alterations in coagulation resulting in thrombosis and disseminated intravascular coagulation are clearly linked with permeability edema, but whatever causal relation might lie within the link has not yet been explained (1, 5).

Clinical Expression. The hallmark of ARDS is hypoxemia refractory to oxygen therapy. The hypoxemia, a direct consequence of inadequate oxygen exchange from the alveolar epithelium to the capillary endothelium, expresses itself in the patient as progressive dyspnea, tachypnea, and cyanosis. The patient began developing these symptoms on Day 10, four days after chest x-ray and lung scan provided evidence of pneumonia.

The deteriorating arterial blood gases and chest x-rays over the next two weeks confirmed the diagnosis of ARDS. An arterial oxygen tension (PaO_2) frequently below 60 mm Hg despite respiratory support and diffuse, rapidly spreading infiltrates on x-rays ("white lung") together indicate acute pulmonary insufficiency.

The initial problem with alveolar-capillary exchange may be neutrophil-mediated endothelial damage resulting in edema, as discussed above.

The bronchoscopic finding of "many white cells" on Day 9, one day before obvious breathing difficulties appeared, fits nicely with the concept. However, the complex and only partially understood pathophysiology of respiratory failure involves many other important factors as well. These include epithelial destruction, proliferation of cuboidal Type II pneumocytes, shunting and ventilation-perfusion mismatch, thrombosis, reduction in functional residual capacity, fibrosis with a fall in lung compliance, and pulmonary vascular constriction due to the hypoxemia and acidosis (5, 6, 9). The precise causes most likely vary a bit according to the specific predisposing factors (5) and surely are compounded by prolonged oxygen therapy, toxic in its own right (1, 2).

Prevention. Although at least one half of the ARDS patient population dies from the condition, most of those who survive it suffer little residual pulmonary dysfunction (1, 2). This fact underscores the significance of finding effective means of management: We are left with well patients if they survive the acute crisis.

At present the greatest hope for successfully managing the ARDS patient lies in preventing the full-blown syndrome from developing. Thus, Days 6 to 12 were critical in this patient's course. More aggressive treatment might have been appropriate if the upcoming events could have been better predicted. Levels of plasma C5a and the fibrin-fibrinogen degradation product D-antigen may both be elevated in patients with incipient ARDS; assays for these factors are possible methods for identification of ARDS before symptoms appear (1).

Treatment modalities may work much more often if instituted early. This applies not only to oxygen therapy, but also to such treatment possibilities as danazol (which elevates serum antiprotease activity) and corticosteroids. The latter are currently under study against ARDS and theoretically promising because they are known to break up PMN aggregates and prevent increased vascular permeability due to endotoxemia (1).

Treatment of the underlying condition that has led or is leading to ARDS represents at least as crucial a challenge as attempting to correct the ARDS itself. This patient's respiratory problem developed in association with a fever of unknown origin. By Day 16 the infection had led to a classical septic-shock picture, with persistent fever, severe hypotension, and high cardiac output. Although evidence of bacteremia could not be documented in over fifteen cultures, it was assumed that antibiotics inhibited bacterial growth, and the patient was treated as septic. Many points of the antibiotic management here are open to question. For instance the aminoglycoside, rather than being discontinued on Day 6, might have been tapered to a dosage low enough to cause a drop in serum blood urea nitrogen and creatinine levels. It is also unfortunate that a serum endotoxin assay was not available. Without one, gram-negative septicemia remained only a presumptive diagnosis.

Evidence from a 1982 study that human J5 antiserum substantially reduces mortality from septic shock caused by gram-negative bacteremia raises the hope of treating this condition far more successfully (13). Thus the prognosis of ARDS, often precipitated and most likely sustained by sepsis, might greatly improve. When an intravenous preparation of J5 antiserum is developed, its use in cases of suspected instead of confirmed bacteremia will need to be clarified. The possibility of antiserum therapy might well increase the utility of the endotoxin assay as a diagnostic tool.

Earlier, more effective means of treatment are a promising goal, but primary prevention is still better. Anesthesiologists have been researching ways of reducing respiratory complications, particularly following upper abdominal operations. A 1981 British study suggests that combining heated, humidified air with methoxyflurane to maintain anesthesia may help to prevent postoperative pulmonary problems (14). While this single finding with an experimental group of only 20 patients awaits corroboration, the general direction of preventive research is encouraging. An interdisciplinary approach between anesthesiologists, surgeons, and physiologists as well as pulmonary and infectious disease specialists is highly recommended; both more investigations and wider dissemination of their results would be valuable.

Acknowledgments

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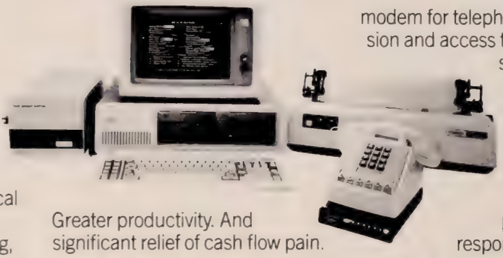

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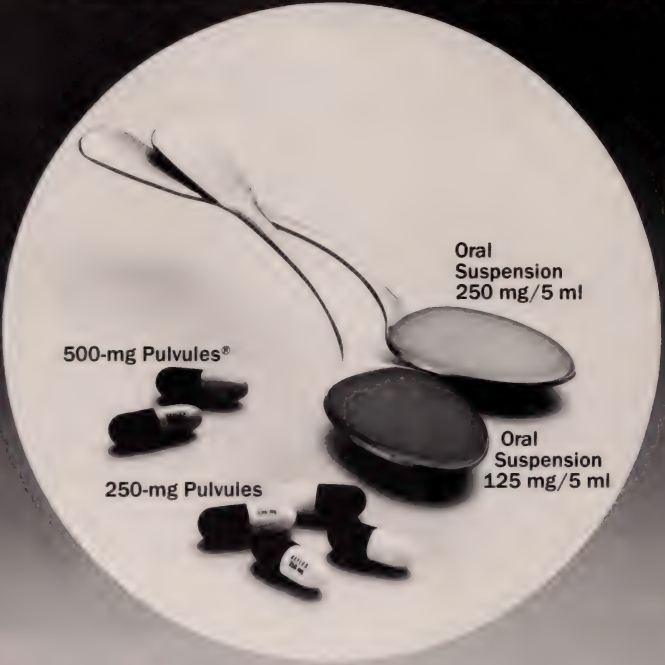
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Volume 51
Number 4
July–August 1984

CONTENTS

GASTROINTESTINAL RADIOLOGY

A FESTSCHRIFT FOR RICHARD H. MARSHAK, MD

Introduction *Jack G. Rabinowitz, M.D.* 311

Comments *Edward B. Singleton, M.D.* 312
James J. McCort, M.D. 312

Richard H. Marshak: An Appreciation *Daniel Maklansky, M.D., Arthur E. Lindner, M.D., and Jerold D. Kurzban, M.D.* 313

SMALL BOWEL

An Overview and Summary of Roentgen Signs of Diseases of the Small Intestine *I. Meschan, M.A., M.D., Hon. D.Sc.* 319

Tuberculosis of the Small Intestine *Jack M. A. Tishler, M.D.* 337

Ileorectal and Ileosigmoidal Fistula in Crohn's Disease: A Clinical-Radiological Correlation *Burton I. Korelitz, M.D.* 341

Diagnosis of Extrinsic Abscesses affecting the Small Intestine *Doon O'Riordan, M.D., and Hans Herlinger, M.D.* 347

Gastrointestinal Carcinoid Tumors: Analysis of 104 Cases *James L. Clements, Jr., M.D., Gordon L. Hixson, Jr., M.D., Robert N. Berk, M.D., Wylie J. Dodds, M.D., and Harvey Goldstein, M.D.* 351

A Pathophysiologic Approach to Nontumorous Small-Bowel Disease *William W. Olmsted, M.D., and Col. Joel E. Lichtenstein, U.S.A.F., M.C.* 360

The Value of Computerized Tomography in Crohn's Disease *Mathis P. Frick, M.D., Erich Salomonowitz, M.D., and Eugene Gedgaudas, M.D.* 368

Intubation Infusion Method: Reliability in Diagnosis of Mechanical Partial Small-Bowel Obstruction *Dean D. T. Maglinte, M.D., and Roscoe E. Miller, M.D.* 372

continued

Cedars-Sinai Medical Center

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GREATER MIAMI

CONTENTS *continued*

Diagnosis of Meckel's Diverticulum in Adults *C. S. Ho, M.D., FRCP (C), J. Shewchun, M.D., and G. R. Greenberg, M.D., FRCP (C)* 378

Small-Bowel Changes Secondary to Intraperitoneal Leakage from Dermoid Cyst of the Ovary *Richard D. Wolfe, M.D., Irwin Weinreb, M.D., and Charles Silver, M.D.* 382

Ultrasound and Computed Tomography in the Evaluation of Inflammatory Bowel Disease *Richard E. Schwab, M.D., and Robert L. Bree, M.D.* 387

STOMACH AND DUODENUM

Treatment of Gastrinoma *Robert M. Zollinger, M.D.* 401

Snail-like Spiral Deformity of the Stomach (Schneckenförmige Einrollung) *Charles H. Lu, M.D., James Olson, M.D., and Edumund A. Franken, M.D.* 404

Single-Contrast and Double-Contrast Radiography in the Detection of Gastritis *Ruedi F. Thoeni, M.D.* 408

The Esophagus and Stomach After Proximal Gastric Vagotomy *Herbert J. Smith, M.D., George Willeford, M.D., and Fred M. Aueron, M.D.* 417

Abnormal Mucosal Fold Patterns in the Duodenum *William B. Seaman, M.D.* 421

ESOPHAGUS AND PHARYNX

Carcinoma of the Esophagus: Its Varied Radiologic Features *Farooq P. Agha, M.D., and Walter M. Whitehouse, M.D.* 430

Adenocarcinoma Arising in Barrett Esophagus: Pathologic and Radiologic Features *Stacey J. Keen, M.D., Gerald D. Dodd, Jr., M.D., and J. Leslie Smith, Jr., M.D.* 442

Steroid-Responsive Dysphagia: A Clue to the Diagnosis of Esophageal Lymphoma *Steven P. Field, M.D., David B. Sachar, M.D., Craig C. Childs, M.D., and Kenneth P. Rubin, M.D.* 451

The Value of the Barium-Swallow Technique in the Evaluation of the Hypopharynx *R. Kristina Gedgaudas-McClees, M.D., and Eric Carr McClees, M.D.* 455

COLON

Single-Contrast or Double-Contrast Barium Enema: A Historical and Philosophical Perspective *Jack R. Dreyfuss, M.D., and Murray L. Janower, M.D.* 461

Post-Ischemic Bowel Obstruction in the Low-Birth-Weight Infant *Edward B. Singleton, M.D.* 465

The Widened Retrorectal Space: Some Radiographic Clinical Considerations *Thomas C. Beneventano, M.D., David D. Frager, M.D., and Ellen L. Wolf, M.D.* 467

continued

CONTENTS *continued*

Continent Ileostomy *Rhona J. Keller, M.D., Mansho T. Khilnani, M.D., Joel J. Bauer, M.D., and Irwin M. Gelernt, M.D.* 473

Oral Barium Tracer: An Adjunct for Barium Enema Preparation *Rubem Pochaczevsky, M.D.* 479

Anterior Pararenal-Space Infection from Colon and Appendiceal Perforation *James J. McCort, M.D.* 482

A Diagnostic Approach to Colon Bleeding *Jerome D. Waye, M.D.* 491

MISCELLANEOUS

Staging of Lymphoma and Testicular Carcinoma *William E. Torres, M.D., and Michael E. Bernardino, M.D.* 502

Life-Threatening Gastrointestinal Complications of Leukemia *Tim B. Hunter, M.D., and John C. Bjelland, M.D.* 508

Radiologic Evaluation of the Portal System by the Newer Modalities of Computed Tomography and Ultrasound *Francis F. Ruzicka, M.D.* 516

A Dozen Pediatric Ultrasonic Donuts *Rita Littlewood Teele, M.D.* 528

Interventional Endoscopy in Diseases of the Biliary Tree and Pancreas *Jerome H. Siegel, M.D., FACP* 535

Splenic Cystectomy and Splenic Preservation *W. John B. Hodgson, M.S., FRCS, FACS* 543

Percutaneous Drainage of Abdominal Abscesses and Fluid Collections *Joseph T. Ferrucci, Jr., M.D.* 547

Entrainment of Microspheres within Blood Flowing through Microarteries *George S. Harell, M.D., Mark Taylor, M.D., Charles C. Berry, Ph.D., Aaron Corbet, Ph.D., and Beverly Bradley, B.S.* 552

Index to Advertisers

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Richard H. Marshak, M.D.

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 51, No. 4, July–August, 1984
Printed in U.S.A.

Gastrointestinal Radiology A Festschrift for Richard H. Marshak, MD

Introduction

It is a personal honor for me to help edit this festchrift dedicated to the memory of Dr. Richard H. Marshak. Dr. Marshak was a dominant figure in radiology for well over thirty years. His diagnostic contributions and his dedication to The Mount Sinai Hospital were instrumental in establishing our department as one of the more renowned in the world. His passing creates a void that will be difficult to fill.

Dick had a great love for The Mount Sinai Hospital and an even greater love for teaching. He was proud of his association with this institution and emphasized his pride continually during his many visiting lectureships. His love for teaching never faltered or diminished despite his almost complete loss of vision, his diabetic neuropathy, and (in his last few weeks of life) osteomyelitis of the foot. During his entire professional career, he conducted a weekly gastrointestinal radiology conference for our residents, and—despite his handicaps—never missed one, and never lost his enthusiasm. He was truly a remarkable teacher. His approach to the diagnosis of gastrointestinal diseases was methodical, precise, and admirable. He could literally caress the film and feel the diagnosis.

Many people saw Richard Marshak as controversial and argumentative. These personality traits are well described by Dr. Singleton. I myself believe that they were his greatest assets and only a façade.

He was never one to accept a fact at face value and loved to discuss and debate. Because of this, he become a major pioneer in the development of concepts and criteria that elevated the small bowel from an untouchable area in diagnostic radiology to a status equal in importance to the remainder of the gastrointestinal tract. Dr. Marshak undoubtedly did have a strong ego. He deserved it. However, when one truly knew him and understood him, one appreciated him as a loyal and devoted colleague with a great sense of humor.

There can be no question that as a physician and radiologist he was universally respected and admired. This festchrift, with contributions by many of his colleagues, friends, and former associates throughout the country, certainly attests to this. We will all miss him. He was a pleasure to watch.

JACK G. RABINOWITZ, M.D.
Professor and Chairman
Department of Radiology
The Mount Sinai Medical Center
New York, NY

The production of this issue was made possible in part by contributions from two anonymous donors.

Comments

Masterful speaker, authoritative teacher, renowned radiologist—all of these terms and many more could be applied to Richard H. Marshak. However, the three ingredients of his personality which I recall most vividly and which impressed me from the time we became friends many years ago were his sense of humor, his remarkable memory, and his courage.

The first of these, his sense of humor, was not known to everyone, because many recall Dick Marshak as being dogmatic, critical, perhaps egotistical, even insulting, characteristics which are all the antithesis of a warm person with a sense of humor. Our friendship began through frequent meetings when each of us was a participant either in a course or a national or international meeting. Through these many meetings I developed a fondness for Dick, and his sense of humor became obvious in many ways. He could not only tell a humorous story but, more importantly, he could take a joke and could laugh at himself. Occasionally while giving a lecture, I would use Dick as the object of a story. Several examples come to mind. One time I referred to him as the "greatest gastrointestinal radiologist in the world—the reason being because Dr. Marshak told me so." On another occasion I referred to Dr. Marshak as "the richest radiologist in the country because he had pay toilets for his barium enema patients." Dick frequently repeated these stories in social gatherings and publicly in his own lectures and apparently took great delight from them.

The second characteristic of his personality which I recall vividly is his remarkable memory. When I was a resident, I attended one of the instruction courses given by Dr. Marshak at an RSNA meeting. Before his course was over, I left the room in order to attend the last part of another prominent speaker's course. At that time, I had never met Dr. Marshak nor did he know me. Many years later, after we were friends, he recalled the time when I walked out of his instruction course. On another occasion, he and I were members of a film reading panel at one of the national meetings and, as usual, he performed brilliantly. After the panel, I asked how he could remain so calm and speak so eloquently in front of a large audience when faced with unknown cases seen only a few hours before. He placed his arm around my shoulder and whispered, "Ed, I was terribly nervous the whole time, but in all of these situations, I memorize everything I say before I am called upon to speak." His memory was indeed phenomenal.

The third and perhaps most important part of Dick's personality was his courage, and I am sure that many contributors to this festschrift will recall this trait. His courage was best exemplified during the last few years while his health was failing and his eyesight rapidly deteriorating. Instead of quitting, he stayed as active as ever and continued to give brilliant lectures describing in detail the slides with Dan Maklansky by his side using the pointer and adroitly assisting him in the case being projected. Indeed, courage is not a strong enough word for his participation and endurance in scientific activities during the last few years.

Edward B. Singleton, M.D.
St. Luke's Episcopal and
Texas Children's Hospitals
Houston, Texas

Knowing the caliber and achievements of Dick's many friends, I anticipate the festschrift will make a significant contribution to our knowledge of gastrointestinal radiology.

My friendship with Dick began about twenty years ago when we had exhibits side by side at the R.S.N.A. As usual, his won the first award. Over the years his lectures and publications have greatly expanded my knowledge of gastrointestinal disease, particularly granulomatous enteritis. At one time, he kindly reviewed the radiographs and offered helpful advice for a colleague suffering from Crohn's disease.

I look forward to reading the festschrift.

James J. McCort, M.D.
Santa Clara Valley Medical Center
San Jose, Calif.

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Richard H. Marshak, M.D. An Appreciation

DANIEL MAKLANSKY, M.D., ARTHUR E. LINDNER, M.D., AND JEROLD D. KURZBAN, M.D.

IN MEMORIAM

Dr. Richard H. Marshak was born in New York City in 1912 and died on December 20, 1982, after a brief illness following a myocardial infarction. For over three decades, he was a commanding figure in gastrointestinal radiology. He was awarded the Bachelor of Science degree by the College of the City of New York, the Master of Arts degree (in anthropology) by Columbia University, and the MD, with honors, from the University of Louisville in 1937.

After Dr. Marshak's residencies in both pathology and radiology in New York City at The Mount Sinai Hospital, Dr. Burrill Crohn, who was at Mount Sinai, invited him to join his private office as a consulting radiologist. This association was maintained for nearly two decades. Dr. Marshak used their extensive clinical material to initiate his investigations into the radiology of gastrointestinal disease. His creativity and talent in diagnostic radiology advanced the specialty of gastrointestinal radiology far beyond what had been envisioned by his predecessors.

The weekly conferences correlating radiological and pathological findings held by Dr. Marshak at Mount Sinai Hospital for over three decades provided a structured schedule for generations of radiology residents and fellows in related specialties.

He was clinical professor of Radiology at the Mount Sinai School of Medicine. He received many honors, many gold medals and citations, and served for a time as president of the American College of Gastroenterology and of the New York Roentgen Ray Society. He wrote many scientific articles and was the senior author of the texts *Radiology of the Small Intestine, Radiology of the Colon,* and *Radiology of the Stomach.*

For many years he presented annual refresher courses at the meetings of the Radiologic Society of North America and the American Roentgen Ray Society. His enthusiasm for education continued to the end of his life; indeed, two days before the onset of his final illness he delivered a postgraduate course to an audience of 1,200 at the Radiologic Society of North America meeting in Chicago.

We grieve for the loss of our friend and colleague. Medicine—gastroenterology in particular—has lost an outstanding contributor and practitioner.

This formal obituary, of the sort published in various periodicals, is a brief biography and a list of contributions, but does not illuminate the man. Merely presenting a bibliography would be a disservice to Richard Marshak. Proud as he was of his accomplishments, he was an individual governed by passions, yet had a rare ability to investigate and approach problems dispassionately.

The more youthful or junior readers of this article will no doubt perceive only hazily the status of gastrointestinal radiology forty years ago, when Richard Marshak first entered the academic scene. Since that time a revolution in roentgen diagnosis has accompanied the many advances in medicine and surgery.

When we examine today the standard textbook on radiology of the gastrointestinal tract published by Templeton in 1940, we find the information it offers sparse indeed. It was in the 1950s and 1960s that Richard Marshak and several of his colleagues established order and promoted the subspecialty of gastrointestinal radiology. He made a significant contribution to the work of rendering comprehensible the radiology of the small intestine. Much of what we now take for

---

From the Department of Radiology, The Mount Sinai School of Medicine of The City University of New York (Maklansky and Kurzban) and the Department of Medicine, New York University School of Medicine, New York, NY.

granted in this specialty was barely recognized forty years ago. Until the mid 1950s, the most frequent diagnosis yielded by the small-bowel examination was "disordered motor pattern."

When Dr. Marshak joined Dr. Crohn in the mid 1940s, Crohn was the most renowned and the busiest consultant gastroenterologist in New York. Whether or not the patients brought their own radiographs, Dr. Crohn would insist that the studies be repeated by his own radiologist, Dick Marshak. Since ileitis was quite literally "Crohn's disease," Dr. Marshak was able to see these patients by the hundreds. This experience prompted his initial descriptions of the radiographic pattern of regional enteritis and inspired his further studies in small-bowel radiology.

In addition to the clinical material provided by his practice with Dr. Crohn, Dr. Marshak also had a commitment to the Consultation Service at Mount Sinai Hospital. Every Monday, Wednesday, and Friday morning from 7:00 AM until 8:30 AM he would fluoroscope patients before going to Dr. Crohn's office. During these 90 minutes he would perform a score of more upper gastrointestinal and barium enema examinations, dashing from room to room wearing the old red goggles and rendering immediate wet readings.

This wealth of clinical experience acquired from Mount Sinai and his own office allowed him to utilize his earlier pathological training to establish an order and understanding of small-bowel radiology. He had that rare talent for recognizing a pattern: to organize data from diverse presentations into a coherent, intelligible description. In fact he would refer to himself almost disparagingly as a "pattern-maker," a term used in the New York garment industry to describe those craftsmen who could create a pattern from which a garment would be sewn. In a similar manner, Dick established a pattern for the recognition of small-bowel disease.

Dr. Marshak was also gifted with two other abilities. He was a charismatic lecturer able to establish an almost spiritual contact with his audience, capturing and holding their attention. Furthermore, he was an excellent writer. Reviewing his papers, articles, and texts carefully, one notes that he avoided excess verbiage. He expunged the "however," the "moderately," and the "slightly" from both his manuscripts and his talks. He never allowed a run-on sentence. He avoided turgid prose and abstruse syntax.

It was his custom to begin a paper or chapter—after weeks of mental preparation—by dictating directly into a tape recorder in a tone close to the conversational. A typist transcribed his dictation overnight. The next day he would sit down and edit. This process continued until he reduced his material to the minimum necessary for a clear, concise presentation and understanding of his subject. Characteristically he never depended on isolated material that required memorization. Nor did he offer elaborate charts and tables. Although he was blessed with a remarkable memory and could retrieve information after many decades, he realized that others were not equally talented. In his presentations, therefore, he always tried to "tell a story," that is, to deliver his thoughts in a sequential, logical, and coherent manner, so that the reader or listener could understand rather than merely memorize.

Dr. Marshak recognized early in his career that there is a natural history, a progression of change, a pathogenesis of disease based on the underlying pathology and anatomy. With each of the wide variety of subjects that he investigated, he sought to develop the pathophysiology of the disease and illustrate it with appropriate radiographs and pathologic specimens. Those who listened to him, who knew him, realize that he never spoke from notes and never read his material. He rarely flashed printed material on the screen. He never presented the same lecture twice in the same manner, just as the concert artist never gives a recital in exactly the same fashion.

Dr. Marshak was a radiological evangelist. He was an indefatigable lecturer. For more than three decades he gave annual refresher courses for the Radiological Society of North America and for the American Roentgen Ray Society. He was a visiting professor at nearly every major university in the United States and abroad. These were not only opportunities for personal satisfaction, but also provided him with access to thousands of students. He was a teacher in every sense of the word, and wherever, he went, he taught. Through this combination of writing and lecturing by example he was able to share concepts that he had evolved after decades of study. He was proudest of being a teacher. He always sought out promising young radiologists as they embarked on their careers and bestowed on them his mantle of support and advice. He encouraged promotions for them, lecture invitations, to them, and publications by them.

The tragic irony in Dick's career was that the insulin-dependent diabetes he developed in his thirties brought progressive deterioration of his vision in his sixties. Paradoxically in this emotional man, he remained unembittered by his fate. Instead of surrendering to his handicap he capitalized on it. The limitation of his physical activities permitted his to reflect at length on topics medical and radiologic. Instead of Sunday golf or tennis he spent his weekends and his evenings pondering, returning to the office in the morning with a wealth of ideas and concepts evolved during the time the rest of us had been disporting ourselves in less productive, but sighted, activities.

His final years were a flurry of intellectual activity. He considered such diverse topics as the future of American economic policies and the significance of aphthoid ulcers; the impact of socialism on Western Europe and the efficacy of the air-contrast enema. With us as co-authors, he added *Radiology of the Colon* and *Radiology of the Stomach* to complete the trilogy that began with *Radiology of the Small Intestine*. To keep abreast of medical intelligence he hired college students to read him the latest journals and textbooks. He studied literature and European history via the books on tapes recorded by the Lighthouse.

Despite his retinopathy, which caused him to lose his peripheral and distant vision as well as his search pattern, he could still discern an isolated image when it was carefully pointed out to him and could then render an accurate diagnosis. Before his visual loss, he was a superb film reader, an individual who would add zest, humor, and accuracy to any film reading panel, always without preparation or prior review.

Rather than restrict this introduction to a recital of Dr. Marshak's contributions, we felt that it would be illuminating to describe some of the highlights of his academic career and to display title pages and illustrations of classic articles produced by this prolific author and investigator.

The Natural History of Ileitis

His initial work was the description, delineation, and presentation of the natural history of ileitis. Before this work of his, no coherent understanding of the radiographic progression of this disease had been presented. In his early papers of the 1950s, Dr. Marshak was able to utilize Dr. Crohn's extensive material and organize what had been a perplexing array of manifestations of ileitis.

It was Dr. Marshak who initiated the concept of ileitis progressing from a relatively acute to a subacute disease without stenosis, characterized by spasm, irritability, thickening of the folds, and superficial ulcerations. There followed progressive alterations in the mucosa, the submucosa, and all underlying coats of bowel; persistent inflammation; and early onset of fibrosis, resulting eventually in severe fibrosis with stricture formation. The coalescence and deepening of the superficial ulcerations produce serpiginous punched-out ulcers, often associated with fistulas and sinus tracts. The title pages of some of his papers illustrate this progression (Figs. 1–4).

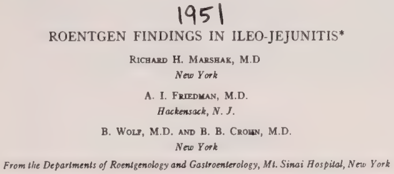

1951
ROENTGEN FINDINGS IN ILEO-JEJUNITIS*
RICHARD H. MARSHAK, M.D
New York
A. I. FRIEDMAN, M.D.
Hackensack, N. J.
B. WOLF, M.D. AND B. B. CROHN, M.D.
New York
From the Departments of Roentgenology and Gastroenterology, Mt. Sinai Hospital, New York

Fig. 1.

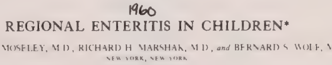

1960
REGIONAL ENTERITIS IN CHILDREN*
By JOHN F. MOSELEY, M.D., RICHARD H. MARSHAK, M.D., *and* BERNARD S. WOLF, M.D.
NEW YORK, NEW YORK

Fig. 2.

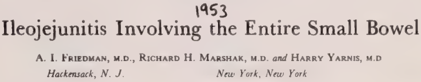

1953
Ileojejunitis Involving the Entire Small Bowel
A. I. FRIEDMAN, M.D., RICHARD H. MARSHAK, M.D. *and* HARRY YARNIS, M.D
Hackensack, N. J. *New York, New York*

Fig. 3.

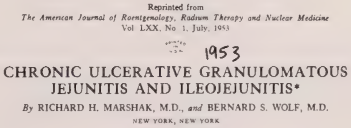

Reprinted from
The American Journal of Roentgenology, Radium Therapy and Nuclear Medicine
Vol LXX, No 1, July, 1953
PRINTED IN U.S.A. 1953
CHRONIC ULCERATIVE GRANULOMATOUS
JEJUNITIS AND ILEOJEJUNITIS*
By RICHARD H. MARSHAK, M.D., *and* BERNARD S. WOLF, M.D.
NEW YORK, NEW YORK

Fig. 4.

He revolutionized the study of the small bowel following an experience with a patient with a history of ileitis. Plain films of the abdomen revealed multiple dilated loops of small bowel secondary to multiple obstructive segments as the result of stenosis and skip lesions. Dr. Marshak hesitated to give this patient barium. Dr. Crohn reassured him and commented that barium would not solidify within the liquid content of the small bowel. Dr. Marshak then gave this patient the standard 6–8 ounces of barium and proceeded to wait in the office with the patient 6, 8, and 12 hours for the head of the barium column to reach the distal ileum and the ascending colon. It was not until 36 hours later that the initial 6 ounces of barium reached the colon.

This type of case suggested to Dr. Marshak that he might utilize large amounts of barium—16, 24, even 30 ounces—in order to maintain a full column and visualize the entire small bowel as a continuous structure rather than studying it in individual segments. This evolution in technique was one of his significant contributions to improving the small-bowel examination.

He confirmed the concept that postoperative recurrence always develops in the bowel proximal to the anastomosis.

Dr. Marshak was instrumental in introducing the concept that Crohn's disease can involve the colon (Figs. 5–7). Although this idea was rejected initially by Dr. Crohn, the definitive paper from London describing Crohn's colitis as distinct from ulcerative colitis did not appear until 1960.

ILEOCOLITIS

Harry Yarnis, M.D., Richard H. Marshak, M.D.
and
Burrill B. Crohn, M.D., New York

Fig. 5.

Segmental Colitis[1]

RICHARD H. MARSHAK, M.D., BERNARD S. WOLF, M.D., and JOAN ELIASOPH, M.D.

Fig. 6.

The Problem of Ileocolitis

RICHARD H. MARSHAK, M.D., and JOAN ELIASOPH, M.D.

Fig. 7.

In addition to his extensive work in ileitis and colitis, Dr. Marshak was one of the earliest contributors to the radiography description of ulcerative colitis. He described the roentgen features of toxic dilatation of the colon, a severe acute complication of that disease (Fig. 8).

MEGACOLON, A COMPLICATION OF ULCERATIVE COLITIS

RICHARD H. MARSHAK, M.A., M.D.,* LOUIS J. LESTER, M.D.*
New York City
AND
A. I. FRIEDMAN, M.D.
Hackensack, N. J.

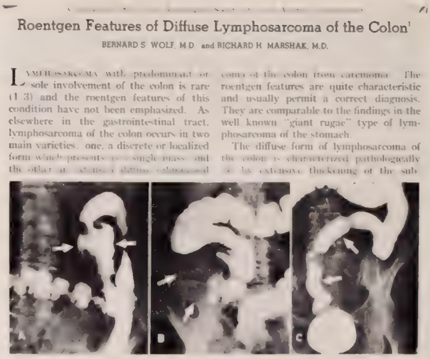
Fig. 8.

In a series of publications, Dr. Marshak was able to correlate the pathologic and radiologic findings in lymphoma of the intestinal tract (Figs. 9, 10). He described the variety of presentations of lymphoma in any portion of the intestinal tract to include five forms:

THE ROENTGEN FINDINGS IN LYMPHOSARCOMA
OF THE SMALL INTESTINE

RICHARD H. MARSHAK, M.D.,
BERNARD S. WOLF, M.D.,
New York, N. Y.
AND
JOAN ELIASOPH, M.D.
Stamford, Conn.

Fig. 9.



Roentgen Features of Diffuse Lymphosarcoma of the Colon[1]

BERNARD S. WOLF, M.D. and RICHARD H. MARSHAK, M.D.

LYMPHOSARCOMA with predominant or sole involvement of the colon is rare (1-3) and the roentgen features of this condition have not been emphasized. As elsewhere in the gastrointestinal tract, lymphosarcoma of the colon occurs in two main varieties, one, a discrete or localized form which presents as a single mass and the other as [illegible] diffuse [illegible] [illegible] coma of the colon from carcinoma. The roentgen features are quite characteristic and usually permit a correct diagnosis. They are comparable to the findings in the well known "giant rugae" type of lymphosarcoma of the stomach.

The diffuse form of lymphosarcoma of the colon is characterized pathologically [illegible] by extensive thickening of the sub

Fig. 10.

- multiple nodular defects
- an infiltrating form characterized by infiltration of the mucosa and submucosa resulting in thickening of the folds
- a polypoid form often resulting in intussusception
- endoexocenteric form with excavation and fistula formation including aneurysmal dilatation
- predominantly an invasive form of the mesentery with large extraluminal masses, single or multiple, with extrinsic compression of the adjacent bowel.

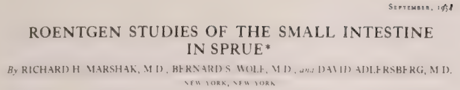
Another of Dr. Marshak's major contributions was his early awareness that submucosal thickening of the small intestine can occur from a variety of causes. This thickening may represent edema fluid caused by hypoproteinemia as a result of protein loss, or thickening due to bleeding or infarction in the submucosa (Fig. 11); or infiltration of the submucosa by neoplasm such as lymphoma or plasma cell dyscrasia. These thickened fold patterns can and should be recognized, and a specific diagnosis can often be made.

Protein-Losing Disorders of the
Gastrointestinal Tract: Roentgen Features[1]

RICHARD H. MARSHAK, M.D., BERNARD S. WOLF, M.D., NATHANIEL COHEN, M.D., and HENRY D. JANOWITZ, M.D.

Fig. 11.

Thirty years ago Marshak et al described the radiologic diagnosis and manifestations of sprue (Fig. 12). He characterized the findings in the small bowel as consisting of dilatation, segmen-



September, 1954

ROENTGEN STUDIES OF THE SMALL INTESTINE IN SPRUE*

By RICHARD H. MARSHAK, M.D., BERNARD S. WOLF, M.D., and DAVID ADLERSBERG, M.D.

NEW YORK, NEW YORK

Fig. 12.

tation and flocculation, and nonobstructive intussusception.

Initial investigations of the roentgen findings in giardiasis led Dr. Marshak to study the immunoglobulin deficiency syndromes and enabled him to describe and differentiate the roentgen manifestations of these diseases. The x-ray findings of giardiasis include spasm and irritability of the jejunum associated with thickening of the folds and with increased secretions. The ileum remains normal. Giardiasis may be associated with immunoglobulin deficiency. The small nodules described are due to nodular lymphoid hyperplasia.

In a series of subsequent publications, Dr. Marshak described the radiographic as well as the clinical manifestations of the immunoglobulin deficiency syndromes. A characteristic finding is the presence of severe nodular lymphoid hyperplasia. Here, the entire ileum is seen to contain multiple small circular nodular defects.

Early on he also recognized the relationship of these diseases to lymphoma and was able to follow several patients from the onset of nodular lymphoid hyperplasia to the development of lymphoma over a period of years.

This briefest of reviews of Dr. Marshak's published works serves at least to illustrate the span of his interests and the scope of his contributions. Richard Marshak had his faults and his foibles, his temper and his tantrums, his ego and his pride, but he also gave of himself unhesitatingly—to his patients, his friends, his proteges, and all of us—by the dissemination of the complex variety of information which he helped to organize. He was devoted to his profession. It is true that he loved to extract the last measure of recognition, that he cherished his accolades and delighted in his many awards and honors. Perhaps he sometimes seemed to be self-serving, but he also served us all by giving of himself in his teaching, his intellectual achievements, and his dedication to medicine.

Small Bowel

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An Overview and Summary of Roentgen Signs of Diseases of the Small Intestine

I. MESCHAN, M.A., M.D., HON. D.SC.

Dr. Richard Marshak spent much of his life studying the roentgen signs of abnormality of the small intestine (1, 2). Here, in commemoration of his work, these signs are categorized in relation to abnormalities of number, position, contour, size, architecture, density, and function. I have tried to cover the gamut of diseases of the small intestine and their objective appearances radiographically in this abbreviated format.

Roentgen examination of the small intestine with the aid of barium sulfate as the contrast agent is currently based on the use of so-called "colloidal" barium. When administered orally, a 50% (weight over volume) mixture of barium sulfate may be employed, but when administered by enteroclysis, usually a 30% (weight over volume) mixture is adequate. Prior to the introduction of the barium, much information can often be gained by a study of the abdominal films. It is most important to recognize that many of the roentgen signs familiar to radiologists before the introduction of "colloidal" mixtures were related to the contrast agent employed; such roentgen signs as "scattering" or even the "moulage" sign were artefacts of the barium mixture rather than true roentgen signs of abnormality.

A classification of roentgen signs of abnormality in the barium-filled small intestine is difficult (3) since so often the basic signs overlap. I previously developed a system of basic roentgen signs (4, 5) which may be applied to virtually all parts of the body, as follows.

- abnormalities of number
- abnormalities of position (although position may normally be variable in the case of the small intestine)
- abnormalities of contour or shape
- abnormalities of size
- changes in the architecture of the small intestine, which may be subdivided according to the internal and external aspects of the small intestine
- density aberrations, such as gas, calcification in the wall of the small intestine, or inspissation in the lumen
- abnormalities of function, inclusive of the malabsorption syndrome
- changes with respect to time and treatment

Frequently, a combination of these signs must be considered. For example, since the category of architecture involves both internal and external patterns, there will be an overlap between the categories of contour and size with architecture. Nevertheless, such cataloging of roentgen signs of the small intestine is worthwhile.

Abnormalities in Number

The most important abnormalities in number in respect to the small bowel are duplication (even triplication) or the formation of enterogenous cysts. The latter (Fig. 1) are usually not connected with the bowel, contain a clear fluid or a fluid of mucoid consistency, and are subject to complications such as volvulus and intussusception. This kind of cyst may often be recognized by displacement of contiguous bowel.

Ultrasonography and computed tomography, among the newer imaging modalities, assist greatly in this diagnosis.

Abnormalities of Position

There is a high degree of variability in the position of the small intestine since it is attached by a relatively small mesentery obliquely in the abdomen to the retroperitoneum (Fig. 2). The

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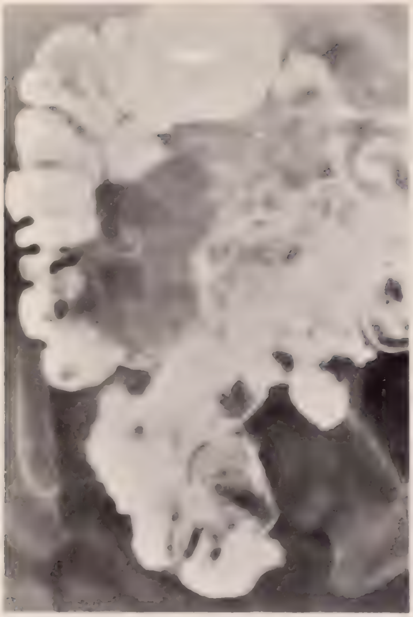


Fig. 1. Enterogenous cyst: ileal duplication cyst impressing itself on ileocecal region—not filling with barium.

small-bowel mesentery attaches to the intestine from the midportion of the descending part of the duodenum to approximately the midportion of the transverse colon. Commonly, the entire intestine rotates into a position in which the ascending colon, descending colon, and rectum are retroperitoneal; the jejunum occupies a position largely to the left of the ligament of Treitz and to some extent extends over to the midabdomen; and the ileum is situated for the most part in the right upper quadrant beneath the right lobe of the liver and descending into the pelvis minor, the terminal ileum rising out of the pelvis minor to join the cecum in the right lower quadrant. Quite often, however, one observes the "common" mesentery deformity in which the colon is situated in the left lower abdomen and the small intestine is in the upper (Fig. 3). This is the reverse of a normal situation (Fig. 4). And there are various other abnormalities of rotation, particularly of the colon. Thus, the ascending colon may be hyperrotated or nonrotated, in which case the cecum may be found in an aberrant position.

The most important positional abnormalities of clinical significance are anomalies of intestinal rotation (volvulus), especially in the infant; internal herniation; and displacement by contiguous structures. More than one-half of the internal herniations relate to the region of the ligament of Treitz and the paraduodenal fossae or the lesser omental bursa (Fig. 2).

Anomalies of small-bowel rotation are principally limited to the midgut, extending from the midportion of the second part of the duodenum to the midportion of the transverse colon. The most common problem is actually incomplete rotation rather than the "common" mesentery deformity.

In the infant, anomalies of rotation are readily recognized by a barium-enema examination. The cecum is either partially nonrotated or excessively rotated in toward the left midabdomen. Very often, there is an associated abnormality of blood supply. If such an anomaly is asymptomatic in infancy, in the adult it will rarely produce symptomatology. However, in the child, even minor abnormalities in the position of the cecum and ascending colon may bring about mechanical obstruction.

Internal herniation includes particularly the paraduodenal hernia and hernias into the lesser omental bursa, which comprise over one-half of the internal herniations encountered (Fig. 5).

Because of its relatively small attachment to the retroperitoneum and considerable length, the small intestine is subject to displacement. Displacement defects may be produced by the pressure of an adjoining mass or abnormality, such as enlarged mesenteric lymph nodes (caused by inflammation or a neoplasm), matted loops of large intestine, pelvic cysts and tumor, enterogenous cysts (Fig. 1), or omental or peritoneal cysts. Retroperitoneal mass lesions may also displace the small intestine significantly.

External herniation of the small or the large intestine, or of both, usually accompanies a weakness in the wall of the peritoneum. These hernias are usually inguinal, femoral, umbilical, or through surgical scars (ventral).

Both internal or external herniations may lead to incarceration, strangulation, and infarction of small intestine—with clinical symptomatology of complete mechanical obstruction.

Abnormalities of Contour or Shape

Those abnormalities of contour of the small intestine which are associated with architectural changes are described in conjunction with architectural pathology. Otherwise, diverticula, both true and false, and pseudodiverticula constitute

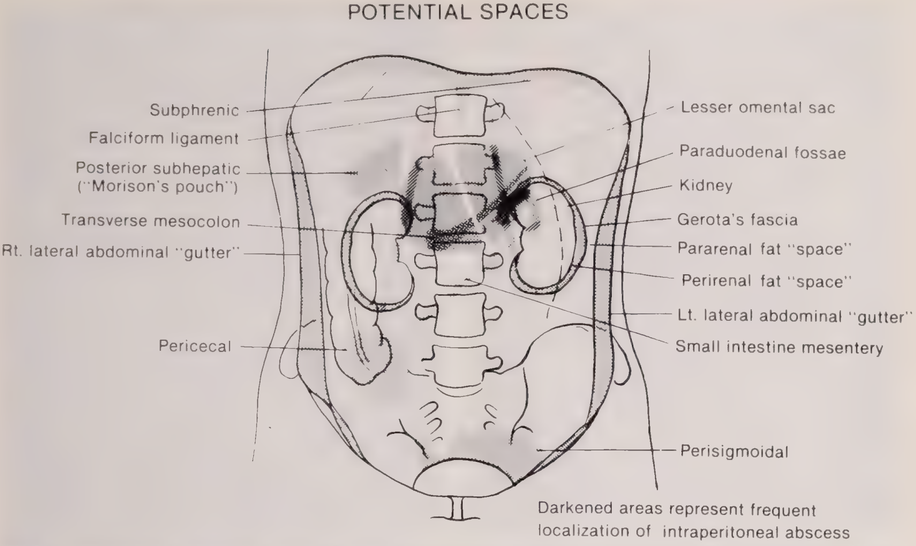

POTENTIAL SPACES
Subphrenic
Falciform ligament
Posterior subhepatic ("Morison's pouch")
Transverse mesocolon
Rt. lateral abdominal "gutter"
Pericecal
Lesser omental sac
Paraduodenal fossae
Kidney
Gerota's fascia
Pararenal fat "space"
Perirenal fat "space"
Lt. lateral abdominal "gutter"
Small intestine mesentery
Perisigmoidal
Darkened areas represent frequent localization of intraperitoneal abscess

Fig. 2. Retroperitoneal attachment of small intestine and potential spaces for retroperitoneal accumulation of abscesses or internal herniae.

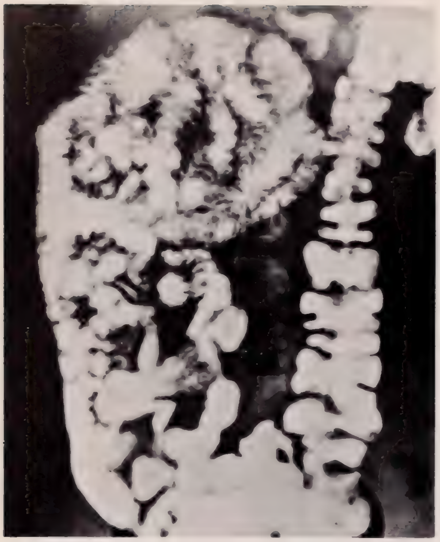
the most important variants from the normal in this category.

False diverticula result from a defect or weakness of the muscular wall of the duodenum, jejunum, or ileum, where mesenteric vessels and nerves pass through into the mesentery. These defects are loci of weakness at which protrusions occur and appear as saccules from the mesenteric lumen into the mesentery. Duodenal false diverticula are approximately ten times more frequent than those involving the jejunum and ileum; and, in general, diverticulosis is more frequent in elderly individuals. Pathologically, diverticula dissect into the fatty tissues of the mesentery. They contain no muscular coats or else very thin strands of muscle (Fig. 6).

In rare instances, diverticula are the site of intestinal stasis, with an overgrowth of certain bacteria that utilize excessive quantities of vitamin B_{12}, producing a pernicious-anemia-like syndrome. Under these circumstances, a blind-loop syndrome may become apparent clinically. Occasionally, neoplasms are found within such diverticula, and they become the sites of intestinal bleeding or inflammatory perforation.

A true diverticulum, consisting of all of the walls of the small intestine, is usually a persistent vestigial remnant of the omphalomesenteric duct, giving rise to a solitary diverticulum about 30 cm from the ileocecal valve. This is called Meckel's diverticulum, and may vary in size and shape from a fibrotic cord to a huge pouch. Such diverticula differ from the composition of the small intestine in that in about half of the cases they contain heterotopic rests of gastric mucosa. Gastric mucosa is subject to peptic ulceration, penetration, and even perforation with the formation of diverticulitis and abscess. Even pancreatic rests may occur in Meckel's diverticula and may be associated with Zollinger-Ellison syndrome, but this is infrequent.

Another important alteration in contour is that which associates with scleroderma. The alimentary tract is involved in about one-half of the patients with this condition, and atrophy of the muscle layer of the small intestine, with fibrous replacement, may occur at any level of the gut (although it is most severe in the esophagus). Even the mucosa may become thin and ulcerated, and the lamina propria and submucosa may contain excessive amounts of collagen. A loss of villi and microvilli, and at times a malabsorption syndrome, ensues (described below under Abnormalities of Function). The vessel walls of the intestine so involved contain perivascular infiltrates with marked collagenous thickening. As a result,



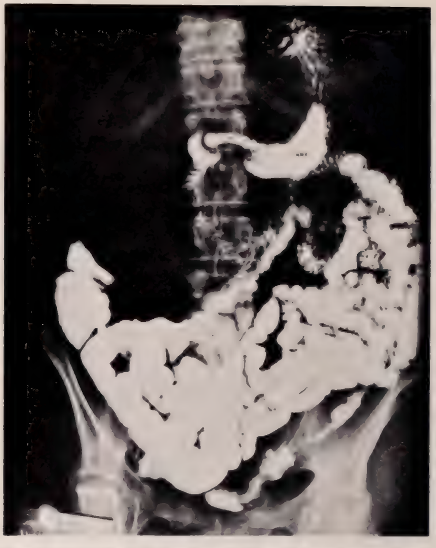


Fig. 3. **Left** Common mesentery deformity: small intestine largely cephalad to line of attachment of small bowel mesentery; small intestine cephalad to it.

Fig. 4. **Right** Normal small intestine caudad to line of attachment of small intestinal mesentery.

pseudodiverticula develop, especially in the large intestine and (rarely) in the small intestine. Since scleroderma produces alterations in architecture, an example of it is shown in that section.

Abnormalities of Size

Abnormalities of size often accompany changes in the architecture of the small intestine, and hence it is desirable to consider size and architecture together. Alterations in size and architecture may be classified as follows.

- dilated loops of small intestine with splayed-out (but not thickened) folds of Kerckring (valvulae conniventes)
- diminished size, often associated with a pattern of mucosal thickening and even intramural thickening to the point of complete stenosis, atresia, and mechanical obstruction
- submucosal thickening, with minimal or no dilatation but readily recognized by computed tomography

This complex of subjects is treated below under Abnormalities of Architecture.

Abnormalities of Architecture

Dilated Loops of Small Intestine with Splayed-Out Folds of Kerckring. Two outstanding examples of this alteration are mechanical obstruction and paralytic ileus.

Mechanical obstruction is often related to strictures, either congenital or acquired (as in potassium enteropathy); atresias; obstruction from gallstones passing through the gastrointestinal tract; foreign bodies in the small intestine; adhesive bands or kinks; hernias; volvulus; intussusception, as occasionally in Peutz-Jeghers syndrome (6); and abscess formation. Or mechanical obstruction may be vascular in origin, with mesenteric, arterial or venous thrombosis (Figs. 7–10). Incidentally, the "colon cut-off sign" (Fig. 7) may be produced by other entities as well, such as superior mesenteric artery thrombosis; carcinoma of the pancreas invading through the transverse mesocolon; annular carcinoma of the colon in this location; toxic dilatation of the large intestine, such as occurs with idiopathic ulcerative colitis.

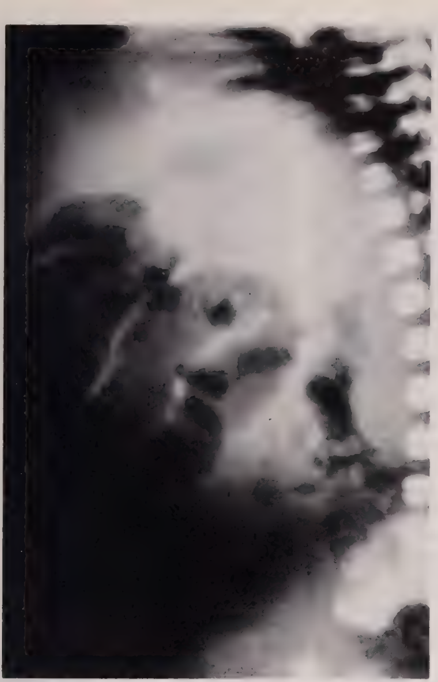


Fig. 5. Internal herniation into paraduodenal fossa, lateral view only. This was associated with vascular abnormalities of superior mesenteric artery and vein.

The most frequent causes of small-intestine obstruction in adults are as follows (7).

hernia (often strangulated)	44%
adhesions and bands (often postoperative)	30%
neoplasms (primary or secondary)	10%
intussusception	5%
volvulus	4%
mesenteric thrombosis	3%
miscellaneous (including gallstone ileus)	4%

Although the distribution of such causes varies in different series, this listing, from a series of 335, is highly representative. Hernias and adhesions cause approximately three-quarters of all cases.

In neonates the most frequent causes of small-intestine obstruction are atresia of the duodenum, jejunum, or ileum; atresia of the colon, rectum, or anus; aganglionosis (Hirschsprung's disease); annular pancreas; midgut volvulus; and internal herniation (8). Additional congenital defects and ischemic necrosis are often present (4).

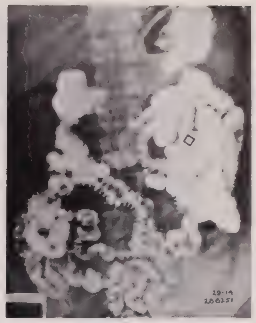
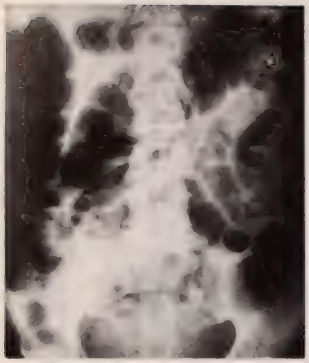


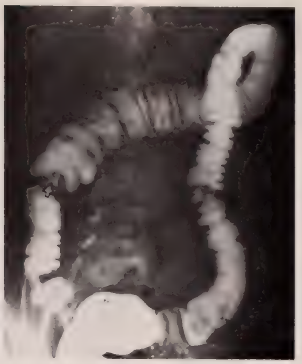
Fig. 6. Diverticulosis of small intestine.

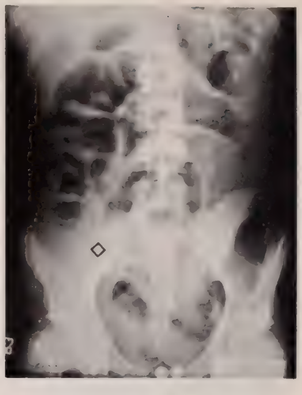
That alterations in the small intestine which can lead to mechanical obstruction may be related to certain forms of irritating pharmaceuticals has long been known (9). For example, potassium and thiazide diuretics may cause a local toxicity, especially in the jejunum. There ensues focal hemorrhage, congestion, and fibrous thickening of the mucosa, with scar formation and annular fibrosis narrowing the bowel and even producing mechanical obstruction. During the formative phases of these alterations, the process may resemble regional enteritis.

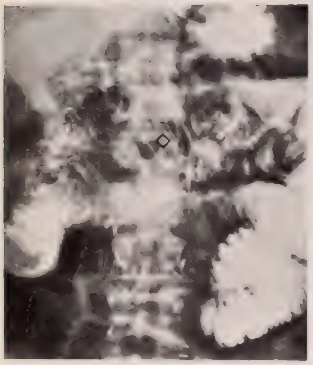
Paralytic ileus may usually be differentiated from mechanical obstruction by the following: (a) total involvement of the entire gastrointestinal tract, and a specific area of obstruction is not identified; or (b) only minimal to moderate increase in diameter of the bowel due to involvement of the small intestine by a reflex process usually in response to sudden pain elsewhere in the body. (c) When the bowel examination is done with the patient in the erect position, there are usually no fluid levels because the absorptive function of the small intestinal mucosa is unimpaired. (d) The bowel wall is usually thin and not thickened. (e) The folds of Kerckring remain delicate in appearance.

The presence or absence of air/fluid levels does not necessarily represent an all-inclusive distinguishing factor between mechanical and paralytic ileus (10). But the so-called string-of-beads appearance of the air/fluid levels is usually a definite indication of mechanical obstruction. The "beads" are small bubbles of air trapped in the folds of Kerckring along the superior wall of the small bowel when the patient is placed in the erect position, even though there may be few, if









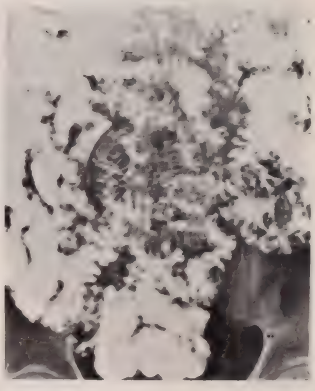


Fig. 7. Upper left "Colon cut-off" sign producing obstruction of large and small intestine. Adhesions at distal end of transverse mesocolon (open arrow) causing colon cut-off sign in relation to chronic pancreatitis.

Fig. 8. Above Intussusception of hamartoma of small intestine in patient with Peutz-Jeghers syndrome of ileocolic type.

Fig. 9. Upper right Appendiceal abscess (open diamond) and peritonitis producing adhesions with partial small-bowel mechanical obstruction and peritonitis, which produces increased thickness of mesentery between dilated loops of small intestine.

Fig. 10. Left Vascular insufficiency producing splayed-out and dilated appearance of jejunum. Patient had had embolectomy from superior mesenteric artery, splenectomy, and sympathectomy.

Fig. 11. Right Amyloidosis of small intestine. *Courtesy of Dr. Gerald Friedland*

any, fluid levels. This apparently does not occur in a "reflex" ileus (Table).

Dilated Loops with Marked Mucosal Thickening. This usually is indicative of an infiltrative process in the small bowel, such as amyloidosis (Fig. 11). Similar changes may occur in ulceroinflammatory diseases, as well as with neoplasia at times. The example par excellence, especially in deference to Dr. Marshak, is Crohn's disease. Here, there is usually a transmural inflammation (Fig. 12) with all layers of the bowel involved to the serosa; fistulation occasionally; noncaseating granulomas; dilatation or sclerosis of the lymph channels; and lymphoid aggregates may be anywhere in the bowel wall. Malignant lymphomas are particularly apt to be associated with this kind of appearance. These conditions are described further below.

Dilated Loops, Thick Walls and Folds, Minimal Dilation. Marshak and his associates in 1967 (11) pointed out that submucosal thickening and minimal or no dilatation of loops of bowel with intestinal edema was found especially with congestive heart failure or constrictive or chronic pericarditis (5). The mucosal thickening and dilatation of the folds are readily apparent. When older types of barium are used, the intestinal secretions, which are excessive in these instances, are probably the cause of the artefactual scattering and clumping of the barium. The folds are thick and appear blunted, incomplete, and irregular. (The condition may resemble sprue, except that in sprue the folds tend to be thin and the dilatation itself is much more marked, as emphasized by Marshak.) The bowel wall, if differentiable, is thickened by the edema, and its motor

TABLE

Radiologic Criteria for Differentiation of Paralytic Ileus and Mechanical Obstruction

Radiological criteria	Paralytic (adynamic) ileus ("Post-op distention")	Mechanical obstruction
Degree of distention	none to moderate	moderate to marked
Distribution of gas and fluid	local to generalized	local to generalized
Amount of intralumenal fluid	none to moderate	moderate to marked
Length of fluid levels	short to medium	short to long
"Discrepancy" signs	infrequent	common
Pneumoperitoneum	persists longer than one week (peritonitis)	usually disappears in one week
Resolution with nonsurgical treatment	often	often (most obstructions incomplete, temporary)
Show point of obstruction		
plain films		occasionally
opaque medium		frequently
Intramural gas	occasionally (ischemia, infection)	occasionally (simple or strangulating obstruction)
Marked distention of single viscus	stomach, cecum, sigmoid	volvulus stomach, cecum, or sigmoid
Pseudotumor	absent	occasionally
"Fixation" of loop	absent	occasionally

activity is irregular and altered. A somewhat similar appearance is found with the protein-losing enteropathies (Fig. 13). Here, although the effacement is not prominent, the folds are thickened. Microscopically, this is shown to be due to a marked dilatation of the lacteals by fat-laden cells in the villi, especially the villi of the jejunum.

The effacement of the small-bowel pattern and thickening of the wall may be well demonstrated by computed tomography in patients with malignant lymphoma (Fig. 14).

A stacked-coin appearance is also strongly suggestive of a hemorrhagic infiltrative process in the wall of the small bowel or of infarction (Fig. 15).

There may be a generalized submucosal thickening, either inflammatory or of neoplastic, chemical, or metabolic origin. This is seen with regional enteritis, tuberculous enteritis, eosinophilic gastroenteritis (Fig. 16), and neoplasias, especially of the lymphoma category. Gamma-globulin disorders accompanying congestive heart failure, hyperalbuminemia, and hyperuric

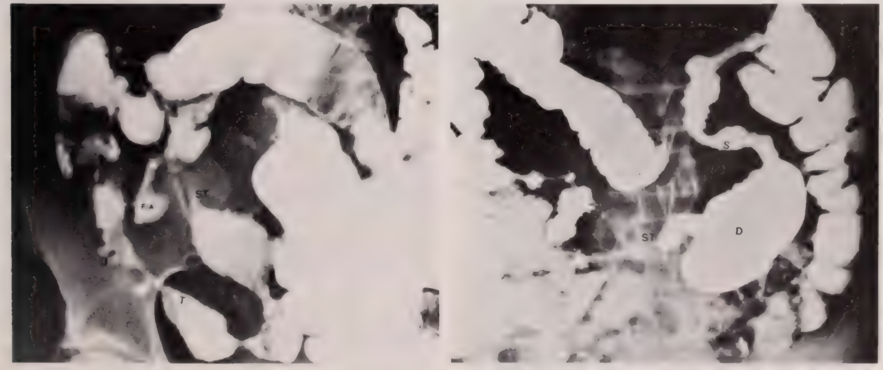
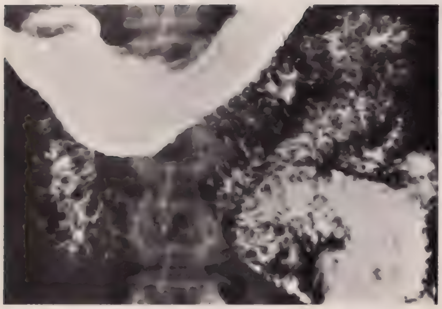
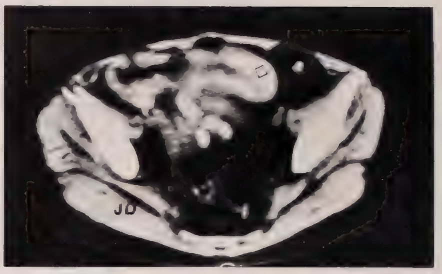
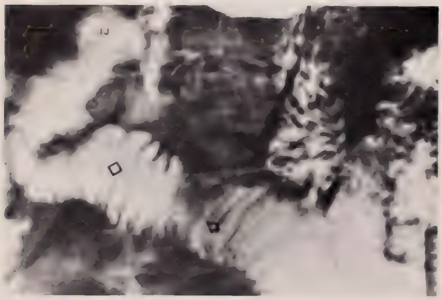
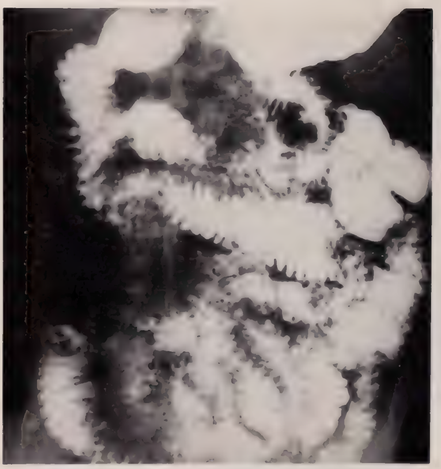


Fig. 12. Regional enteritis. **Left** Submucosal thickening (T), ulceration (U), scar formation (ST), fistulation and abscess formation (F-A). **Right** Submucosal thickening (S), partial obstruction from stenosis (ST), ulceration (U), and dilated segments (D).









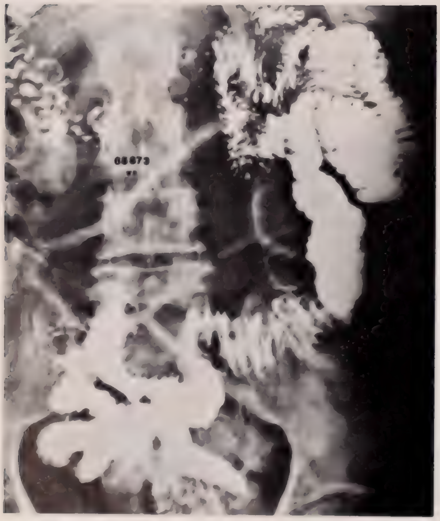


Fig. 13. Upper left Protein-losing enteropathy.

Fig. 14. Upper right CT demonstrating effacement of gastrografin-filled small intestine and thickening of wall of bowel in a patient with lymphosarcoma.

Fig. 15. Center left Ischemic jejunum with hematochezia. Note stacked-coin (diamond) appearance and nodular impression of intramural hemorrhage (open arrow).

Fig. 16. Center right Eosinophilic gastroenteritis involving small intestine. *Courtesy of Dr. Henry Goldberg, University of California, San Francisco*

Fig. 17. Left Whipple's disease.

acid states also may produce this appearance (Fig. 13). A generalized mucosal-type thickening with minimal or no dilatation also occurs with lymphangiectasia or Whipple's disease (Fig. 17). Whipple's disease is an unusual and rare small-intestine disorder in which there are rod-shaped bacilli visualized between cells and within glycoprotein-laden macrophages containing PAS-positive granules. The infection may be treated effectively by antibiotics, particularly penicillin, tetracycline, and chloramphenicol (12). In the classic case, there is a thickening of the wall of the small intestine, and thickening and induration of the mesentery. The intestinal villi are distended and blunted by the histiocytes, sometimes giving to the intestinal mucosa the appearance of a shaggy rug. Other organs, such as the spleen, liver, lungs, kidney, and central nervous system, are frequently affected. Even the heart may be affected by nonbacterial vegetation on the cardiac valves. Most of these patients have a classic malabsorption syndrome, with arthralgia, joint swelling with lymphadenopathy, and skin pigmentation. The diagnosis is best established by small-intestine biopsy.

Absence of Dilation. In the absence of dilatation in the small intestine, the diagnosis rests upon the demonstration of total effacement of the small-bowel pattern, such as may occur particularly in the duodenum, with nontropical sprue or scleroderma (Fig. 18). It may also occur with edema of the small intestine, particularly when there is obstruction to lymphatic drainage at the root of the mesentery (Fig. 19).

Nodular Filling Defect. Impressive alteration of the small intestine is produced by nodular filling defects in the mucosal pattern. These may be single or multiple; less than 0.5 cm in diameter, or greater; sessile or pedunculated.

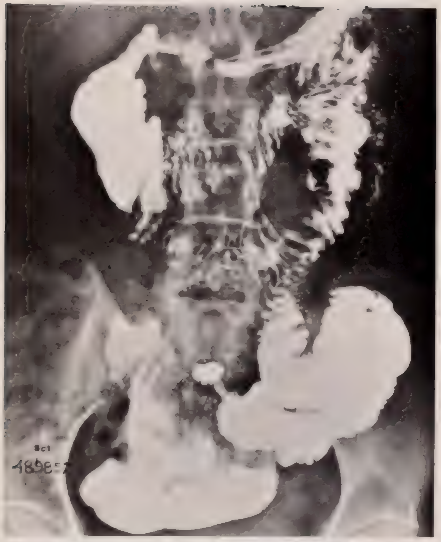
Solitary or multiple nodular defects less than 0.5 cm in diameter (Fig. 20) are most frequently due to areas of lymphoid hyperplasia. In children, very often there is a dimpling centrally within the elevated lymphoid follicle. Peyer's patches in the terminal ileum are especially apt to become manifest in this fashion (Fig. 20). Other causes, however, must be considered, such as carcinoids, malignant neoplasms, and metastatic carcinomas. (Usually the malignant neoplasms involve not only the wall of the small intestine but also the adjoining mesentery.)

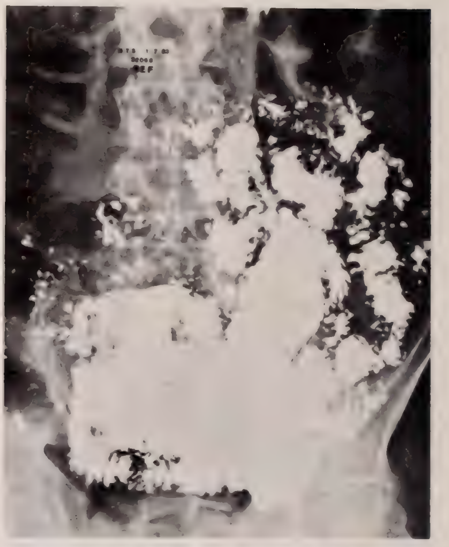
Small-bowel benign tumors, although rare, must be considered too. Among these rare tumors, the adenoma is probably the most frequent. Others are leiomyomas, lipomas, fibromas, angiomas, neurofibromas, and heterotopic pancreatic rests. They are usually recognized clinically by partial intermittent mechanical obstruction, hematochezia, intussusception, and volvulus. It is the larger lesion, however, which produces volvulus (described below).

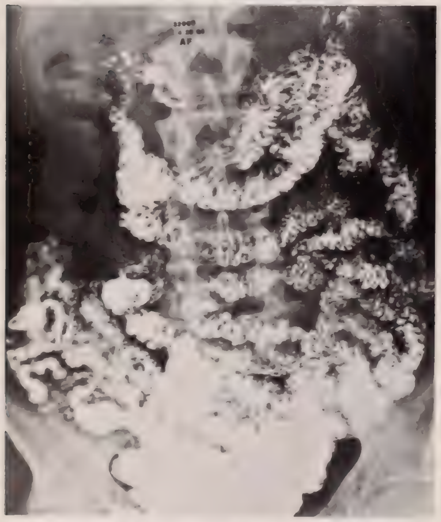
The carcinoid of the small intestine often metastasizes and thus is not a benign tumor. It is usually greater than 0.5 cm in diameter. The carcinoid has also been called the argentaffinoma and is in the family of APUDomas (*a*mine *p*recursor *u*ptake *d*ecarboxylation), neuroendocrine tumors which apparently produce amine and polypeptide hormones. They have a very versatile secretory capacity. The carcinoid has metastatic potential and has been well classified for reference by Tischler (13).

The carcinoid is found in the appendix in approximately 35% to 45% of cases; in the small intestine in 20 to 25%; in the rectum in 15%; in bronchi in 12%; and in the large intestine (excluding the rectum) in 10% (14). In the gastrointestinal tract, carcinoids produce serotonin, histamin, bradykinin, prostaglandins, and possibly other agents as well. Grossly, they are small, round or plaquelike, submucosal lesions usually approximately 4 or 5 cm in diameter, and multiple (about 25% of cases). The overlying mucosa is usually intact, although it may become ulcerating or polypoid and penetrate the bowel to the mesentery. The lesion may spread to regional nodes, the liver, lungs, and bones. When metastatic to the liver, a carcinoid syndrome may ensue which involves the vasomotor system, intestinal hypermotility, bronchoconstriction, cardiac fibrosis and valvular deformities, and hepatomegaly. When there is involvement of only the stomach, small intestine, or colon (except for the rectum), five-year survival is approximately 50% (14). Although the point is highly debatable, in about 16% of the cases involving the small intestine, there may be a concurrence of carcinoid with other cancers elsewhere.

Nodular defects altering the architecture of the small intestine and greater than 0.5 cm in diameter are usually neoplastic in origin, most frequently metastatic. One of the most common of these in my experience is the malignant melanoma (Fig. 21). Whether single or multiple, the malignant melanoma has a tendency to grow concentrically, become hemorrhagic centrally, and give rise to the bull's-eye appearance. Other malignant neoplasms in the category of nodular filling defects include carcinoids, usually submucosal, in the ileum, and multiple in about one-







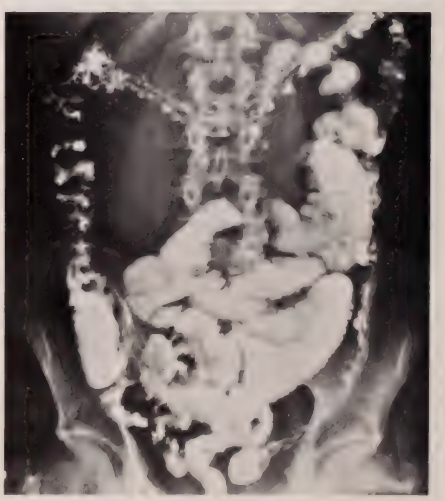


Fig. 18. **Upper left** Scleroderma. Note total effacement of duodenum. Nontropical sprue may do this also. **Upper right and lower left** Nontropical sprue before and after treatment. **Upper right** Before: 1-7-63. **Lower left** After: 4-20-64.

Fig. 19. **Lower right** Edema of small intestine due to retroperitoneal lymphoma obstructing lymphatic drainage; no involvement of small intestine in lymphoma. Small-bowel folds are effaced and swollen due to edema. *Courtesy of Dr. Robert Stevenson*

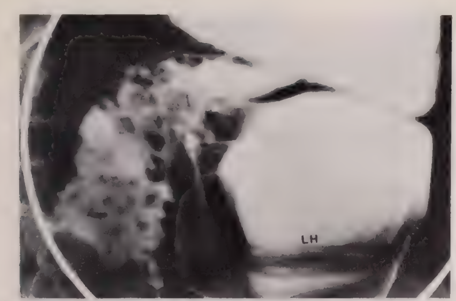


Fig. 20. Lymphoid hyperplasia of terminal ileum (patient in prone position).

third of the cases; adenocarcinomas (see also below), usually in the proximal small intestine and usually fairly well demarcated, with a napkin-ring appearance; and lymphomas, which may be either mucosal or submucosal, involve the distal bowel more frequently than the proximal bowel, and which have a highly variable appearance (see discussion below). Lymphomas tend to be infiltrative, producing considerable dilatation of the bowel, or they may displace various loops of bowel. Leiomyosarcomas may be either intraluminal or both intra- and extraluminal, and may occur anywhere in the small bowel, but usually are large mass lesions, often ulcerated, with demonstrable niches.

With regard to the nodular lesions, both large and small, other processes should be mentioned: intestinal lymphangiectasia; mastocytosis; Waldenström's macroglobulinemia; hyperplastic Brunner's glands in the duodenum; and the Cronkhite's Canada syndrome. With mastocytosis, unlike lymphangiectasia, intestinal secretions are not excessive, and about one-half of these cases have an associated hepatosplenomegaly, sclerotic bone lesions, and associated urticaria pigmentosa.

Waldenström's macroglobulinemia usually entails diffuse nodular involvement of the small bowel, and its appearance resembles Whipple's disease or lymphangiectasia so closely that ordinarily it cannot be radiologically differentiated.

In Cronkhite's Canada syndrome the patient has multiple polyposis, not only of the small intestine but the stomach as well. The syndrome represents a mucosal hyperplasia, usually with other phenomena such as alopecia, nail atrophy, and hyperpigmentation.

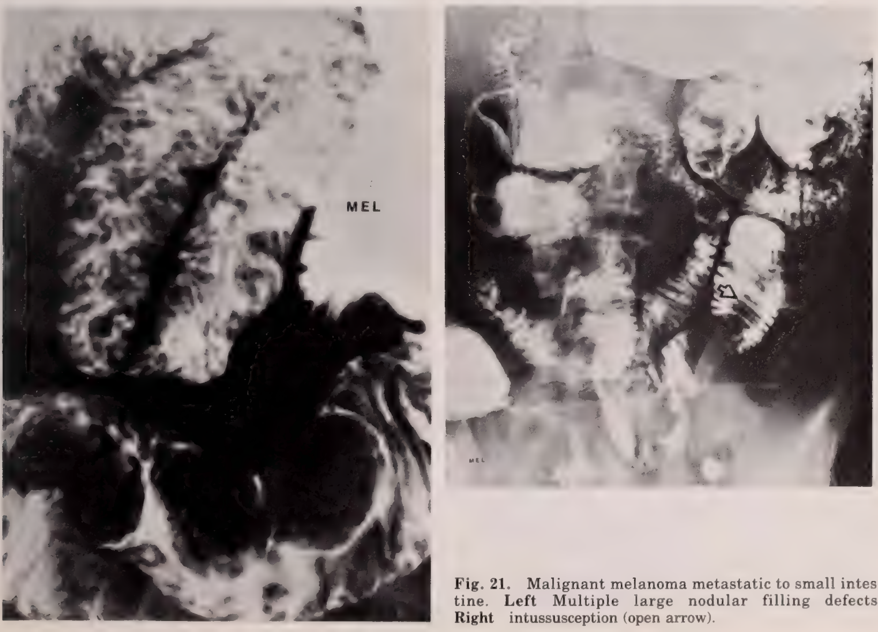


Fig. 21. Malignant melanoma metastatic to small intestine. **Left** Multiple large nodular filling defects. **Right** intussusception (open arrow).

Peutz-Jeghers syndrome (6) is particularly apt to produce large polypoid filling defects of the mucosa and submucosa (Fig. 22) throughout the entire gastrointestinal tract, but particularly in the small intestine; the syndrome is also associated with melanin pigmentation of the buccal mucosa, lips, and digits. The "polyps" represent hamartomatous overgrowths rather than true neoplasms. They certainly rarely give rise to cancer, but are frequently associated with intussusception; this intussusception, however, is not often associated with necrosis of bowel (15).

Lymphosarcomas of the small intestine produce submucosal thickening with multiple small and large filling defects (Fig. 23); in addition, there are other manifestations of this disease, well demonstrated by Marshak and his associates (16). There may be splaying and dilatation, with a coiled-spring appearance due to infiltration of the wall of the small intestine (Fig. 23). The large sausage-shaped appearances are due to diffuse infiltration and dilatation of the small intestine and complete effacement of the normal valvulae conniventes. There are also annular constrictions, similar to those frequently associated with adenocarcinoma of the jejunum.

There are also endoexoenteric forms of lymphosarcoma and leiomyosarcoma (Fig. 24) in which the main manifestation is not so much the nodular filling defect within the small bowel itself, but rather the mass lesion extrinsic to the bowel, often with a connecting fistula or ulceration. The large mass formation produces a displacement of adjoining abdominal organs and sometimes even produces intestinal obstruction. The patient in Fig. 24 had other manifestations of abnormality in the small intestine; dilated folds with effacement of some of the folds were also present. The architectural appearance of nodular filling defects, associated possibly with rigidity of bowel, would suggest a through-the-wall phenomenon, with involvement of the serosa and perhaps the mesentery as well.

"Thumbprinting" from intramuscular hemorrhage may also be categorized as nodulation. (Recall that intramuscular hemorrhage can also produce a coiled-spring appearance).

Ulceroinflammation, Tacking, and Kinking. The diseases that may cause these abnormalities are, in order of likelihood: pancreatitis in the duodenum; carcinoids; metastatic carcinoma; inflammatory processes, such as regional enteritis, tuberculous enteritis and peritonitis (Fig. 25). The ulceroinflammatory diseases which tend to produce this appearance, apart from Crohn's disease, are actinomycosis; acute ileitis; pseudomonas; salmonellosis; shigellosis; staphylococcal infections; and tuberculosis. Actinomycosis may entail a fistula to the exterior abdominal wall. I have mentioned vascular lesions of the small intestine manifested primarily by either the coiled-spring appearance or a nodular effacement of the folds (Fig. 15). The nodular effacement produced by mesenteric thrombosis has also been called "thumbprinting" (Fig. 26), and usually is related to an intramural hemorrhage in association with the thrombosis. Approximately 60% of the thromboses are arterial in origin and may be either embolic, thrombotic, or due to blood stasis, especially in patients who are arteriosclerotic. In about 40% of patients, thromboses are venous in origin. Some vascular lesions are due to a fibromuscular hyperplasia of the mesenteric arteries—although this disorder is much more common in renal arteries.

Occasionally acute hemorrhagic enteropathies will be manifest in this manner as well.

Mesenteric thrombosis may also occur and infarction may result with hernias.

Radiation enteritis or postsurgical thickening of the wall of the bowel, with adhesions or kinking, may also produce phenomena similar to those I have described for other entities.

An annular napkin-ring deformity, with complete destruction of the mucosa and sharp shelflike margins at each end of the napkin ring, is particularly associated with primary malignancy of the small intestine. In the jejunum, this is usually an adenocarcinoma (Fig. 27). This appearance may be simulated, however, especially in the ileum, by a lymphosarcoma.

Almost like the napkin ring but not nearly as shelflike is the type of ragged enteritis which I have seen associated with disseminated lupus erythematosus. This simulates regional enteritis very closely (Fig. 28) and can hardly be differentiated except by its other clinical manifestations.

Narrowness or Tapering to Complete Obstruction. An infarcted appendix epiploica can produce complete mechanical obstruction of the small intestine (Fig. 29) due to the reaction in the immediate vicinity of the appendix. Appendices epiploicae that undergo infarction may become necrotic, hemorrhagic, or form an abscess.

Abnormalities of Density

Abnormalities of density in respect to the small intestine include: gas in the small-intestine wall

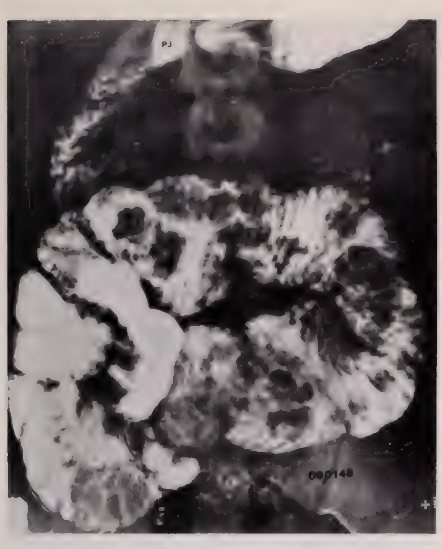


Fig. 22. **Upper left** Peutz-Jeghers syndrome.

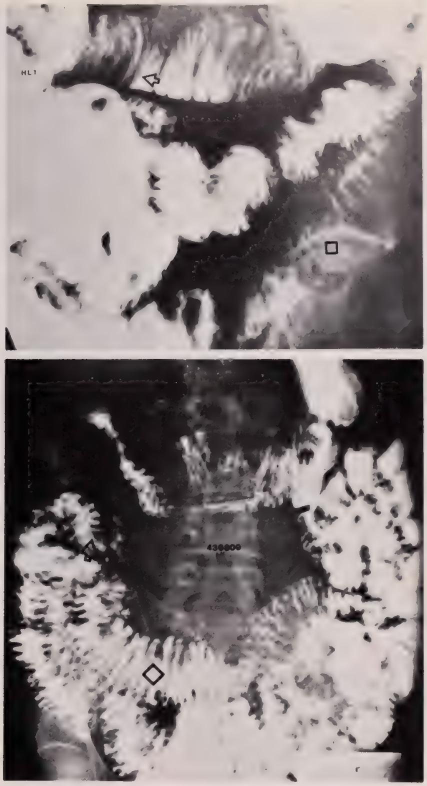
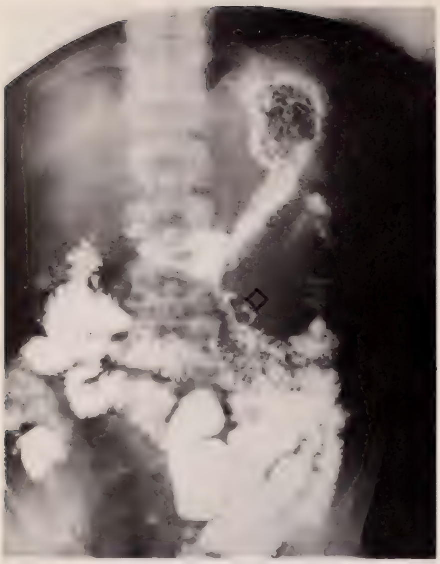


Fig. 23. Lymphosarcoma of small intestine. **Upper right** Multiple filling defects with histiocytic lymphoma; filling defects (open arrow); dilation and splayed appearance (diamond). **Lower right** Occasional less prominent filling defect (open arrow), but thickened valves of Kerckring (diamond).

(pneumatosis intestinalis); fatty or soaplike materials, particularly in relation to necrotizing pancreatitis; calcifications in the small-bowel wall; in the non-contrast-enhanced abdomen, abnormal densities within the small (and large) intestine lumen, with mucoviscidosis or a mucus plug syndrome.

Gas in the small intestine occurs particularly with necrotizing processes in the infant (necrotizing enterocolitis) or with superior mesenteric thrombosis in the adult (Fig. 30). In the infant, the cause is usually unknown, but it may be associated with Hirschsprung's disease or there may be a break in the mucosal continuity, with a dissection of air under the mucosa of the gastrointestinal tract (17). Some instances have been reported as occurring with pulmonary disease, harsh cough, and pneumomediastinum (18, 19). In children, the gas pockets are frequently found in the submucosa, whereas in adults, these pockets are most frequently in the subserosa. In the newborn, gas may be a manifestation of exudative necrotizing enterocolitis and is a reflection of severe disease (20). Spontaneous pneumoperitoneum sometimes occurs as a complication. It is readily recognized primarily by two findings: longitudinal or vertical accumulations of air in scattered foci within the bowel wall proper; or a "bubbly" appearance scattered throughout the entire area of the abdomen, intermixed with the barium shadows of the small intestine. With acute hemorrhagic pancreatic necrosis, there is an enzymic release and destruction of pancreatic substance with an escape of pancreatic enzymes into the adjoining tissue. These enzymes cause focal areas of fat necrosis in



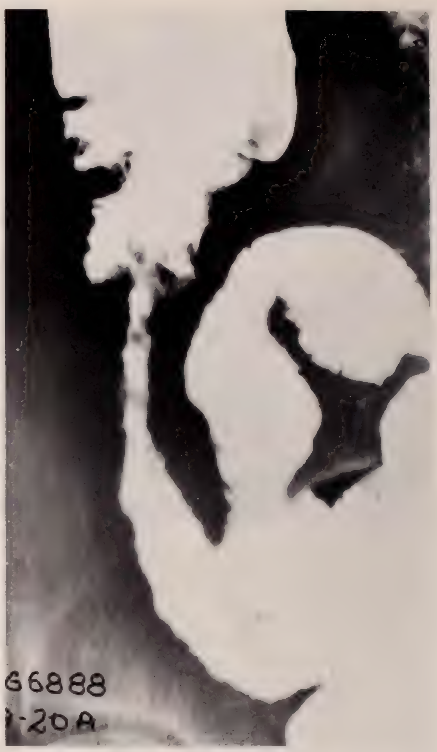
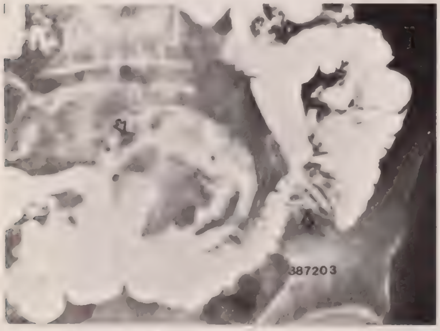


Fig. 24. **Left** Leiomyosarcoma of jejunum. Nodulation, fistulation, and endoexoenteric mass formation (diamond).

Fig. 25. **Right** Regional enteritis with "cobblestone" defects and rigidity of terminal ileum.

the pancreas and mesentery. The two predominant etiologic factors are biliary tract disease and excessive alcohol intake. From the morphology of acute pancreatitis, proteolysis, lipolysis, and hemorrhage are the three major pathologic changes which occur. There is a conversion of fatty acids to soap particles which become intermixed with the other elements. The fatty necrosis



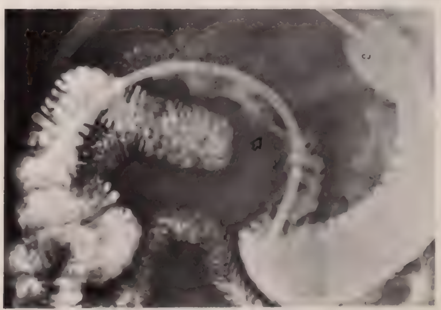


Fig. 26. **Left** Nodular appearance of mesenteric thrombosis, sometimes called "thumbprinting" (open arrow).

Fig. 27. **Right** Annular "napkin-ring" (open arrow) deformity of jejunum due to adenocarcinoma.

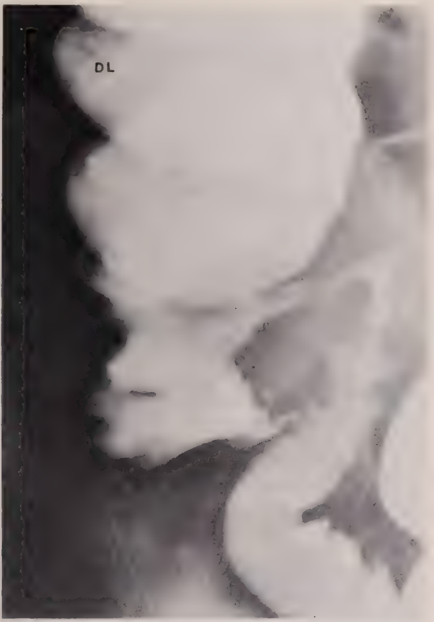
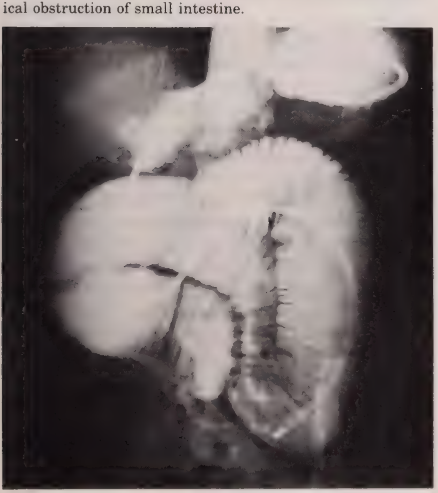


Fig. 28. "Ragged enteritis" due to disseminated lupus erythematosus simulating regional enteritis.

Fig. 29. Infarcted appendix epiploica with complete mechanical obstruction of small intestine.



and soap formation impart a bubbly gaslike appearance in an amorphous distribution over the pancreatic bed itself and the adjoining areas. Late cases have a superimposed suppurative peritonitis.

Another unusual gaseous formation, seen on plain films without contrast media, is related to worm infestation, usually by ascariasis (Fig. 31). On plain films, the multiple worms are outlined by bowel air, either in linear masses or whirls, or in axial projections where a single worm can be seen in linear projection. Very often, in the child, there is opaque pica in the gastrointestinal tract in association with ascariasis, ileus from partial mechanical obstruction, and usually an eosinophilia of a significant degree (greater than 10%). When barium is introduced, it enters the gastrointestinal tract of the worm, making the worm infestation outstanding, particularly when the coiled worms are producing a partial obstruction of the small intestine (Fig. 31).

Calcifications in the small bowel occur with hemangiomata, where their appearance suggests phleboliths in the wall of the small intestine, or in the appendices epiploicae of the large intestine.

Alterations in the density of the small intestine may also be produced by foreign bodies; gallstone ileus, when the gallstone is partially calcified; and a condition reported by Brettner and Euphrat (21) called primary enterolithiasis. In this condition, there is a laminated calculus formation, usually resulting from chronic stasis. It occurs in a diverticulum or is proximal to an area of chronic partial obstruction in an associated favorable chemical milieu. It may also be found in Meckel's diverticulum.

Alterations in density of the small bowel of the infant, found without the introduction of contrast media, may appear in conjunction with mucoviscidosis or meconium ileus; or, classically, they appear within the bowel lumen as inspissated masses with a bubbly appearance suggesting fecal material.

Abnormalities of Function

Motor Function. The motor function of the small intestine, or "transit time," is a function of focal and longitudinal bowel contraction. The transit time of barium in the small intestine may be delayed with intestinal malfunction and may accompany many diseases. Apart from the obstructive phenomena already mentioned, one must also consider scleroderma, with its associated arteritis; hypermotility, with spasm; atony, with ileus; regional enteritis; the protein-losing

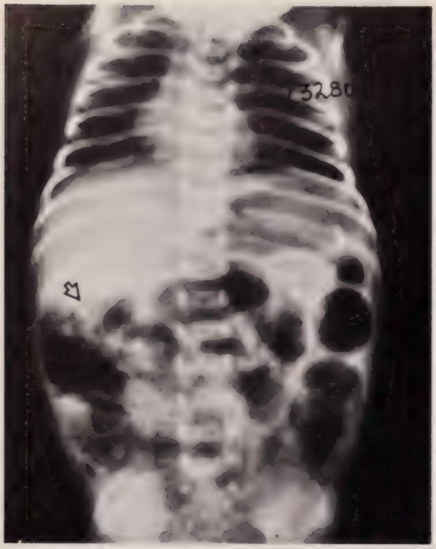
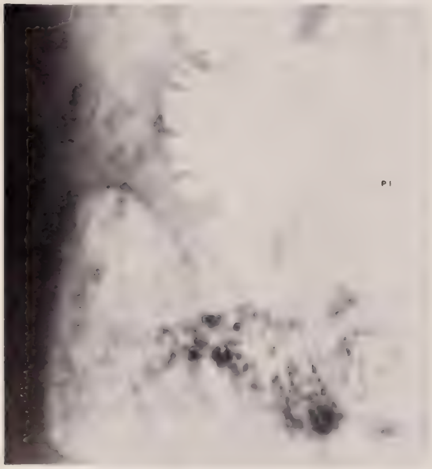


Fig. 30. Above Necrotizing enterocolitis in an infant; intramural air "bubbles" (arrow). **Below** Pneumatosis intestinalis in an adult.



enteropathies; Whipple's disease; the malabsorption syndrome (discussed below). In patients without renal disease, the transit time may be hastened in small-intestine examinations, without alteration of the architecture of the small intestine, by the intravenous injection of 10 mg in 2 cc volume of metoclopramide (Reglan) when the barium has reached the midjejunum.

Absorption. The malabsorption syndrome consists of a variety of very dissimilar mechanisms (22), which may be abbreviated as follows: problems of intraluminal digestion; mucosal-cell abnormality; abnormalities in transport across the mucosa; lymphatic obstruction; defects resulting from previous treatment, such as partial gastrectomy, ileal resection or bypass, or radiation therapy; infection, with infectious enteritis or parasite infestation (and, in certain parts of the world tropical sprue would be in this infectious category); unexplained etiologic mechanisms, such as nontropical sprue (Figs. 18, 32), hypogammaglobulinemia, carcinoid, diabetes, mastocytosis, and thyroid malfunction or malfunction of the thyroid-adrenal-parathyroid axis; drug-induced malabsorption.

From the radiologic standpoint, malabsorption syndromes may be discussed under four main categories: celiac disease and the closely related nontropical sprue; Whipple's disease; disaccharidase deficiency; abetalipoproteinemia.

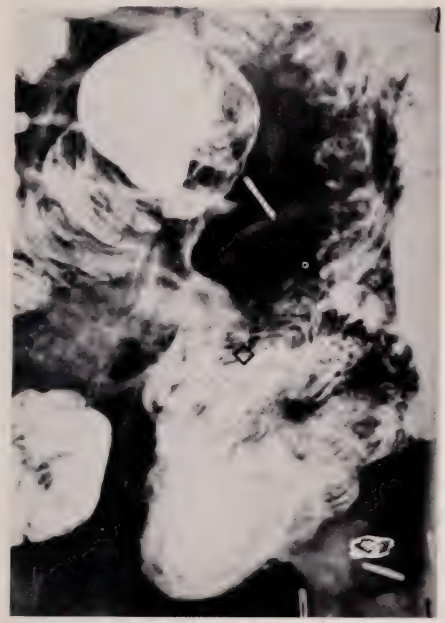
Celiac disease and nontropical sprue are gluten-induced enteropathies exhibiting a hypersensitivity reaction to gluten and gliadin, a reaction that produces IgA and IgM antigliadin antibodies. There is striking loss of the villi of the small intestine, with a smoothness in contour of the small bowel. As pointed out by Marshak, the folds of Kerckring, where they persist, are not thickened or infiltrated (Fig. 18).

Whether patients with celiac disease or nontropical sprue have an increased tendency toward lymphoma formation is an unresolved question.

Whipple's disease consists of arthralgia, joint swelling, lymphadenopathy, and changes in skin pigmentation and the central nervous system. The disease predominantly affects Caucasian men in their fourth and fifth decades, with a male-to-female ratio of ten to one.

Disaccharidase deficiency is largely a mucosal alteration in which lactases appear to be most important. It is apparently a milk and milk-product sensitivity. It may appear in adults, and a viral and bacterial infection may be superimposed. Radiologically, the appearance can be provoked by the introduction of milk or milk products in the barium.

Abetalipoproteinemia is a familial, autosomal, recessive disease process. Patients are unable to synthesize the betalipoproteins necessary for transport of triglycerides from mucosal cells, and it is characterized histologically by lipid vacuola-



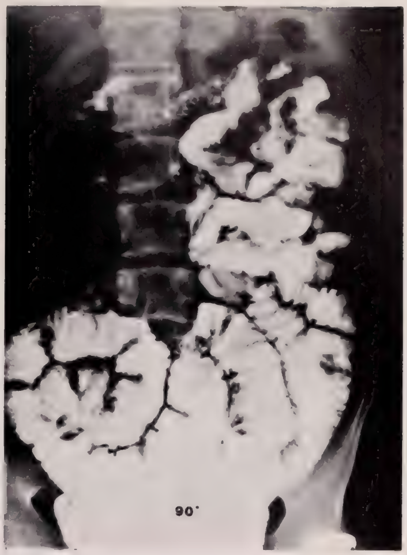


Fig. 31. Left Worm infestation. Barium in gastrointestinal tract of worms (diamond) produces coiled appearance of worms. In this case, worms are producing partial small-bowel mechanical obstruction.

Fig. 32. Right Nontropical sprue.

tion. There is fat contained in the stool and there is hypolipidemia.

Changes with Time and Treatment

These have already been addressed in respect to appropriate treatment of nontropical sprue. Radiation changes which occur in the bowel depend upon the dose administered and the time observed. Radiation first alters the cells of Lieberkühn in the small bowel crypts, preventing their normal replication process. Ultimately, a denudation of the bowel occurs, with ulceration or perforation. Changes resembling those of regional enteritis or ulceroinflammatory disease ensue. Thus, a spectrum of alterations is observed, closely dependent upon the individual history. None of the changes may be considered pathognomonic.

Acknowledgments

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Tuberculosis of the Small Intestine

Jack M. A. Tishler, M.D.

Tuberculosis of the small intestine is uncommon in North America, but in underdeveloped regions of the world, it is one of the more common causes of inflammatory disease of the small intestine (1–7).

Series of 18 Cases. I report experience with 18 cases of clinically or histologically documented small-intestine tuberculosis seen at two large medical centers in the period 1967–1982.

The patients ranged in age from 18 to 65 years, mean, 42 years. There were ten men and eight women in the series. Twelve patients were undergoing treatment for active pulmonary tuberculosis when a diagnosis of small intestine tuberculosis was established. Five patients had a past history of pulmonary TB, and, in 1 patient, pulmonary TB was first suggested on routine chest radiograph one day following an abnormal upper gastrointestinal examination.

All patients complained of abdominal pains; except for one patient with duodenal tuberculosis, the pain tended to be vague and was present for several weeks before the patient sought medical help for the problem. Eight patients presented with signs and symptoms of distal small intestine obstruction, all requiring surgery. A diagnosis of ileocecal tuberculosis was made in 6 of these patients, jejunal tuberculosis in 1, ileal and jejunal tuberculosis in 1.

The erythrocyte sedimentation rate was within normal limits for 12 patients with ileocecal tuberculosis. In 6 it was just above the upper limits of normal (20–25 mm/hr). The white blood cell count was within normal limits in all patients. One patient with duodenal tuberculosis had hematemesis; 4 complained of red blood in the stools.

On physical examination, findings compatible with intestinal obstruction were found in all 8 patients who required surgery. A right lower abdominal mass was also palpated in 6 of these patients. No other pertinent abnormalities were found on examining the other patients.

Radiographic Findings. Ileal involvement was seen in 12 patients, the adjacent cecum also being involved in 6 (50%). The earliest change observed radiologically was nodularity of the ileum, usu-

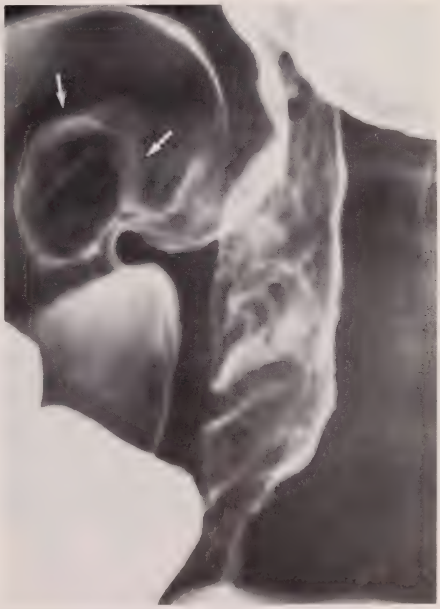

Fig. 1. Man, age 38, with pulmonary tuberculosis and right lower quadrant pain who had had previous appendectomy (arrows). Note numerous nodular impressions in terminal ileum. Ileum developed normal appearance after 6-month course of specific medical therapy.

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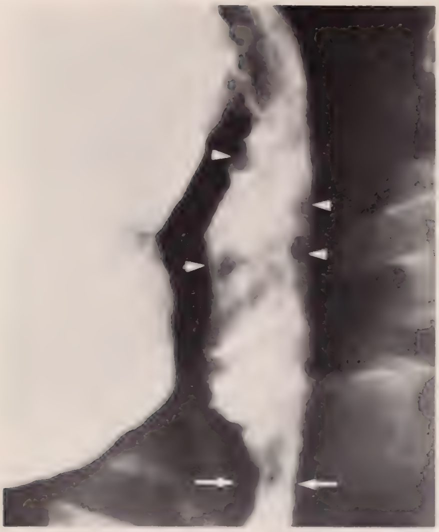
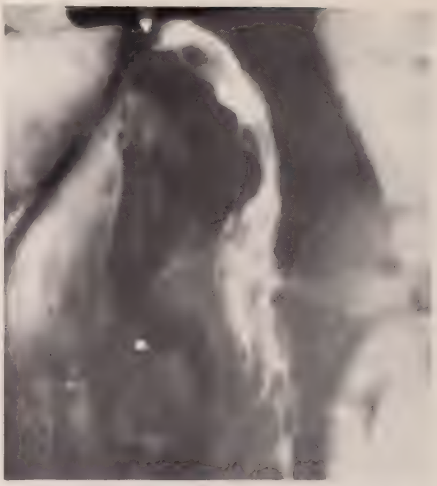




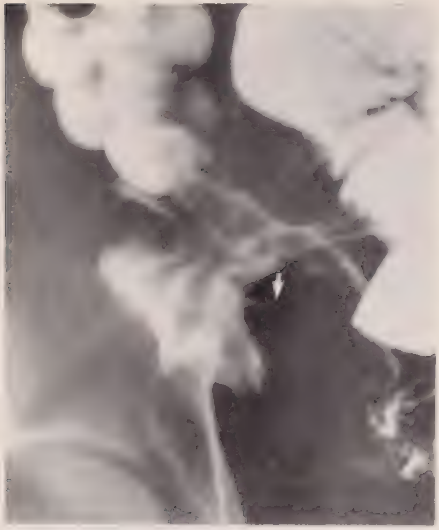


Fig. 2A. Top left Boy, age 18, with active pulmonary tuberculosis and right lower quadrant pain; note submucosal nodules (arrowheads) and narrowed ileum (arrows).

Fig. 2B. Top right Two months later: further narrowing of ileum; submucosal masses are larger; patient still on medical therapy.

Fig. 2C. Left Four months later: stricture of ileum; cecum is now involved. Note sinus (arrow). At surgery, ileocecal tuberculosis was confirmed.

ally a 6–8 cm segment of intestine (Figs. 1,2A). This was seen in three patients; in all 3, endoscopic biopsy via colonoscope confirmed the radiographic impression. Two patients first presented with a 4–7 cm stenotic ulcerated lesion of the ileum which did not respond to intravenous glucagon. Several sinuses were seen in 1 patient (Fig. 2C). A stricture, sinus, and large ulcer was seen in another (Fig. 3). Eight patients presented with obstruction of the terminal ileum (Fig. 4); in one of these, ileal tuberculosis had been diagnosed two years earlier and the patient had been on medical therapy for his intestinal and pulmonary lesion. All 8 were operated on. Active intestinal tuberculosis with caseation was seen in 3, strictures with healed granuloma in the other 5.

Peritoneal fluid was not suspected in any of these patients clinically, but 2 patients had CT scans, and peritonitis was first documented by this method of examination.

The 2 patients with jejunal tuberculosis were undergoing treatment for active pulmonary tuberculosis when a gastrointestinal examination was done to investigate abdominal pain. One patient had a submucosal lesion indistinguishable from a benign submucosal tumor. The other patient had ileal obstruction. Both patients were operated on; the former had isolated involvement of the jejunum, the latter, involvement of the jejunum, ileum, and cecum.

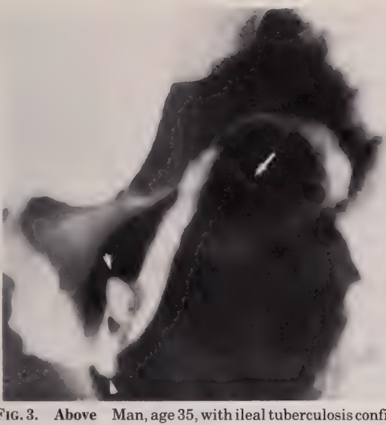


Fig. 3. Above Man, age 35, with ileal tuberculosis confirmed at surgery. Note long area of narrowing, sinus (arrow) and deep ileal ulcers (arrowheads).

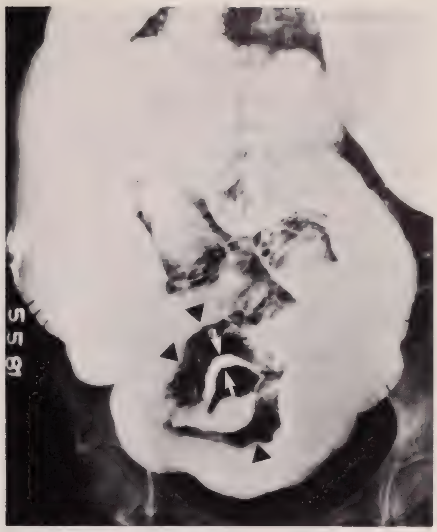
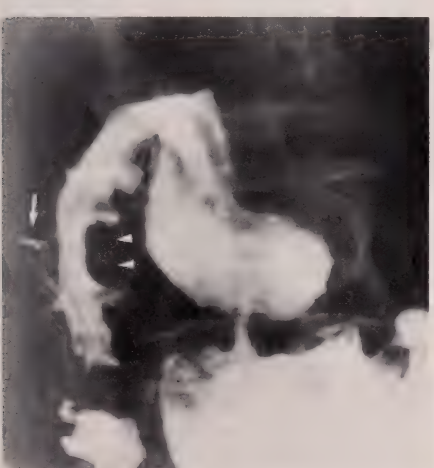


Fig. 4. Right Woman, age 65, who presented with small-intestine obstruction. Examination demonstrates distal small-intestine obstruction with stenosed segment of ileum (arrows) and mass effect (arrowheads). Tuberculosis of ileum confirmed at surgery.

Three cases of isolated duodenal tuberculosis were seen; two of these were previously reported (2). In one case, a large submucosal mass demonstrated in the descending duodenum resolved under appropriate specific therapy. Two other patients had edema and sinus tracts arising from the descending duodenum (Fig. 5A). One of these patients was operated on; the other two improved on medical therapy, with only minor residual deformity (Fig. 5B).

Discussion. Small-intestine tuberculosis has become a rare entity in North America because



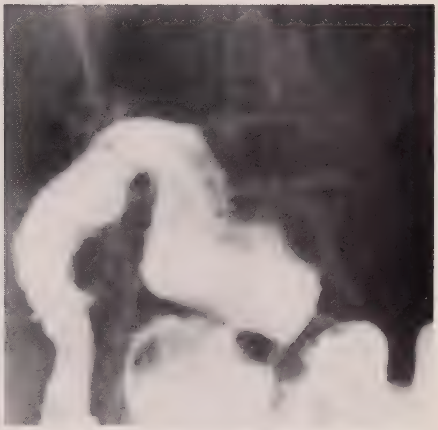


Fig. 5A. Left Woman, age 66, with active pulmonary tuberculosis who presented with hematemesis. Note edema, nodularity, and sinus (arrow) of descending duodenum, and submucosal mass (arrowheads).

Fig. 5B. Right After 2 months of treatment, patient was free of symptoms. Descending duodenum is deformed; submucosal mass, presumably representing a node, persists; edema is less pronounced and sinus less apparent. Duodenum is now normal in appearance at endoscopy.

of advances in public health measures as well as the use of specific medical therapy for pulmonary tuberculosis. The intestinal manifestations of this disease are still common in underdeveloped countries and will probably become more common in the United States following the recent mass immigrations from southeast Asia and the Caribbean, where pulmonary and intestinal tuberculosis is endemic.

The avenue of discrimination of the acid-fast bacilli from lung to intestine is thought to be via ingestion. Sites rich in lymphatics and in relatively prolonged contact with the infected fluids are the primary sites of infection (2, 5). The ileocecal region meets these criteria and is by far the most common site of involvement (5–8). The duodenum and jejunum, having less lymphatic tissue and also less stasis of fluid, are generally spared.

Tuberculosis of the small intestine should be suspected in all patients who have either active or quiescent pulmonary tuberculosis and also have a lesion of the small intestine (2). With the possible exception of immigrants from areas in which tuberculosis of the small intestine is endemic, a normal chest radiograph would make unlikely a diagnosis of small-intestine tuberculosis.

Radiographically, the tubercular lesion resembles Crohn's disease, a submucosal mass, or intestinal adhesions, and, in the patients we saw, a specific diagnosis of tuberculosis could not be made by gastrointestinal examination alone (1–8). Correlation with clinical history and chest radiograph was essential in all cases. Except for the 8 cases that went on to intestinal obstruction at the ileal level and the 1 with duodenal obstruction, all cases responded to specific medication and did well clinically, aside from some deformity of the affected intestine.

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The Ileorectal and Ileosigmoidal Fistula in Crohn's Disease: A Clinical-Radiological Correlation

Burton I. Korelitz, M.D.

Abstract

Clinical and radiological features of 22 patients with ileorectal or ileosigmoidal fistula in Crohn's disease are described. This fistula occurs in approximately 5% of all patients. Reasons for the occurrence of this particular fistula are considered. The onset or recurrence of diarrhea in association with the fistula is often accompanied by relief of obstruction without improvement in prognosis. Constipation, or alternating constipation and diarrhea, with resolution of an abdominal mass correlated best with a favorable response to drug therapy. The fistula itself does not serve as an indication for surgery and, along with the primary bowel disease, often improves on treatment with 6-mercaptopurine.

It is now many years since Dick Marshak first showed me x-rays of patients with Crohn's disease and lectured on his conception of its natural course. Because his personality and convictions were unique, his influence on me has been indelible. Furthermore, rarely in the history of medicine has a radiologist had a combination of opportunity, intense interest and incisive reasoning as to so accurately describe the clinical manifestations of a disease without knowing its cause.

Perhaps the most classic feature of Crohn's disease is the internal or entero-enteric fistula. Though its potential paths are many and vary with the segment of origin, in most cases the fistula arises from the ileum and its direction is predictable. Should it be sufficiently virulent, it will often arrive at the serosa of the sigmoid or the proximal rectum; in some instances the fistula will penetrate the rectum and reach the lumen. Dick Marshak often stated that once this comes about, the patient will be relieved of the obstruction in the ileum by the resulting short circuit (1). This observation, however, has not been documented and other clinical manifestations attributable to the ileorectal fistula have not been reported. In order to describe the radiologic and clinical features of this complication, I present data based on analysis of patients with Crohn's disease who had ileorectal or ileosigmoidal fistulas.

Methods

During the decade from 1972 to 1982 I saw approximately 400 patients with Crohn's disease in office practice. I reviewed the records of these patients to find those with x-ray evidence of ileitis or ileocolitis and ileorectal or ileosigmoidal fistulas. I then studied the x-rays performed before, coincident with, and after diagnosis to identify features diagnostic or presumptive of these fistulas. I analyzed the clinical progress notes for features occurring at or about the time of recognition of the fistula. Similarly, I sought clinical features in the records of patients of the same age with ileitis or ileocolitis but without ileocolonic fistulas for comparison and identification of any features that might occur because of the fistula, as opposed to those independent of it.

Results

I identified 22 patients with ileorectal (18) or ileosigmoidal (2) fistula, or with both (2), seen

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TABLE 1
X-ray Features Related to Ileorectal and Ileosigmoidal Fistulas

Demonstration of fistula	17*
Filling of terminal ileum before left colon on barium enema	4
Filling of rectum before colon on small-bowel x-ray series	7
On both examinations	5
Narrowed or strictured rectum or sigmoid	15
Lumenal disease present	7
Extrinsic disease more prominent than intrinsic	5
Evidence of both	3
Other fistulas from ileum seen by X-ray examinations	10†
Persistent dilation of small bowel	8
Recurrent small-bowel obstruction	4
Persistent air fluid levels	2
Persistent dilation of colon	4

* In one case, only the barium enema was performed.

† Of 6 ileovesical fistulas, 3 were not demonstrated by barium studies.

TABLE 2
Fistula-Related Symptoms in Crohn's Disease (22 patients)

	Pts. with fistula	Controls without fistula
Diarrhea	16	15
Constipation	6	3
Alternating diarrhea and constipation	8	1
Multiple formed stools	3	8
Fever	12	10
Weight loss	9	13
Abdominal pain or cramps	20	19
Nausea ± vomiting	12	6
Bloating or distention	9	2
Abdominal mass	7	1
No diarrhea	7	7

during the ten-year period. In 14 of 22, intestinal involvement with Crohn's disease was limited to the ileum (ileitis); in 5 the ileum and part or all of the colon was involved (ileocolitis); and 4 had recurrent ileitis after an earlier ileocolic resection. The age range at onset of symptoms of the primary bowel disease was 16–62 (mean, 22); the age range at time of diagnosis of the fistula was 20–67 (mean, 31); and the duration from onset of symptoms of Crohn's disease to diagnosis of the fistula was 1–32 years (mean, 8 years). Of the 22 patients, 14 were male, 8 female. Six of the 22 had an ileovesical fistula as well as the ileorectal or ileosigmoidal fistula; all 6 of these were male.

Other fistulas in the 22 patients included:

ileovesical	6	colojejunal	1
multiple ileoileal, ileocecal, or ileoascending	4	rectovaginal	2
		perirectal	3
ileotransverse	1	labial	1
umbilical	1	pararectal	1

A lower abdominal mass was palpable at some time in 7 patients (5 men, who also had ileovesical fistulas; 2 women).

The fistula itself was clearly demonstrated by x-ray studies with barium in 17 cases (Table 1, Figs. 1–4). In 7 cases, it was seen on the small-bowel x-ray but not on the barium-enema examination; in 4 it was seen on the barium-enema but not on the small-bowel x-ray examination; in 5 it was seen in both examinations during the same period of time; and, in one case, only a barium enema was performed. In 5 cases, the fistula itself was not clearly demonstrated on the x-ray examination, but the indirect evidence of its presence was compelling. In these 5 cases, and in an additional 10 cases in which the fistula itself was demonstrable, the x-ray examination showed a segment of rectum, rectosigmoid, or distal sigmoid to be involved, with stricture formation, intrinsic narrowing of the lumen, or extrinsic pressure from an inflammatory mass. In 20 of the 22 cases, the mucosa of the rectal ampulla appeared normal on sigmoidoscopy, while in 2 cases a rectal stricture could be felt with the examining finger.

The symptoms of Crohn's disease in these 22 patients occurred at or about the time of demonstration of the fistula or during the subsequent course. The number of instances of each symptom was compared with the number of the same symptoms occurring in 22 patients, matched for age and sex, with ileitis or ileocolitis but no ileorectal or ileosigmoidal or other entero-enteric fistula. There was no significant difference between the two groups in regard to diarrhea, fever, weight loss, or abdominal pain. On the other hand, constipation, alternating diarrhea and constipation, nausea, vomiting, bloating or distension, and an abdominal mass all occurred much more often in the group with ileorectal and ileosigmoidal fistulas than the group without. Absence of diarrhea per se was noted in the histories of 7 patients with fistulas and also in 7 patients without (Table 2).

All 22 patients were observed for a minimum period of one year following documentation of the ileorectal or ileosigmoidal fistula. The clinical patterns of response or lack of it to drug therapy (ACTH, corticosteroids, sulfasalazine, metronidazole, 6-mercaptopurine) could be determined in

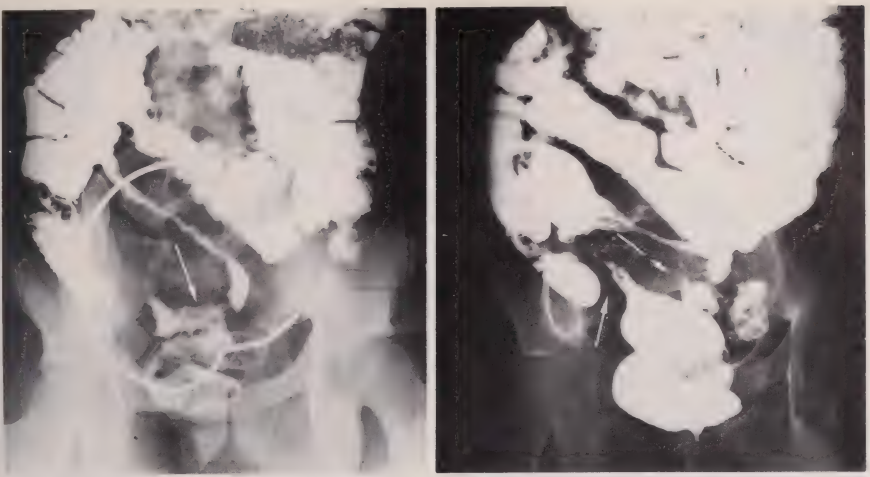


Fig. 1. Left Small-bowel x-ray of patient with known ileitis confirms presence of inflammatory mass in conjunction with strictured ileitis. Barium fills rectal segment and cecum; left colon has not yet been completely filled. Approximation of ileal loop involved with ileitis to rectosigmoid (arrow). **Right** Later small-bowel x-ray of same patient, showing barium entering rectosigmoid and sigmoid at two or more sites from ileitis (arrows). Ileovesical fistula and multiple fistulas in mesenteries are now present as well.

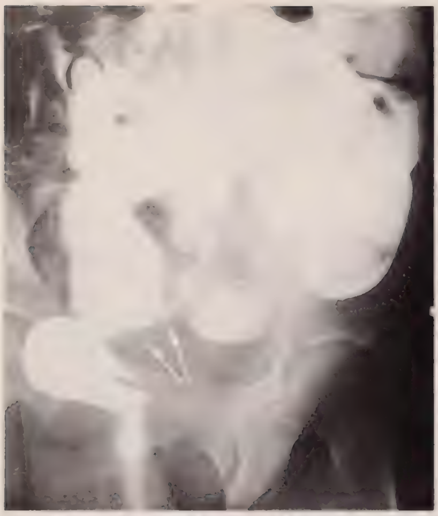
only 13 cases. In four instances, symptoms consistent with bowel obstruction were relieved coincidently with the onset of diarrhea. This pattern could not be attributed to any one drug or necessarily to a drug at all. In the other nine instances, however, improvement occurred coincident with 6-mercaptopurine therapy. These included two patients in whom diarrhea was eliminated and two of the eight instances in which the patient developed a pattern of alternating diarrhea and constipation.

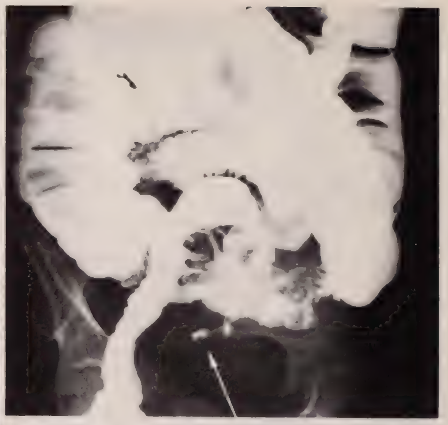
Discussion

In this experience, the incidence of ileorectal or ileosigmoidal fistula as a manifestation of ileitis or ileocolitis is approximately 5%. This figure is similar to that of 3.3% reported by Crohn and Yarnis (2) and probably not different from that found by Greenstein et al (3) and Heimann et al (4). This fistula is unlikely to occur at the time of first symptoms of the primary bowel disease. On the other hand, its occurrence should be expected frequently in the course of Crohn's disease, since the terminal ileum is probably involved in at least 80% of the cases; internal fistulas most commonly arise from the terminal ileum; and the ileum, at some site within a foot proximal to the ileocecal valve, courses close to a segment of distal left colon between the rectum and sigmoid. This fistula apparently develops more often in men than in women. This is best explained by the presence of the uterus in women, which in some patients serves to divert the course of the fistula away from the rectum. In fact, all the patients in this study who had an ileovesical fistula as well as an ileorectal or ileosigmoidal fistula were men. The presence of the uterus probably serves as some protection against development of the ileovesical fistula as well.

Based on the radiologic observations of Marshak (5, 6), the reports of surgeons of their findings at exploration (7), and the results of the dissection of surgical specimens by pathologists, the fistula is encompassed in an inflammatory mass involving the mesenteries. If the mass approximates the distal left colon initially or reaches it while enlarging, the serosal surface of that segment becomes involved. If the inflammatory process then progresses, there is further penetration toward the lumen, and the fistula is completed.

Demonstrating the Fistula. Once the ileorectal or ileosigmoidal fistula has penetrated to the mucosa, it is likely to be capable of demonstration by either a barium-enema x-ray examination or a small-bowel study. The latter, in which the barium must use the same route of transit as that of food and intestinal secretions, should theoretically better show the fistula, and probably does in some cases; however, the distension caused by





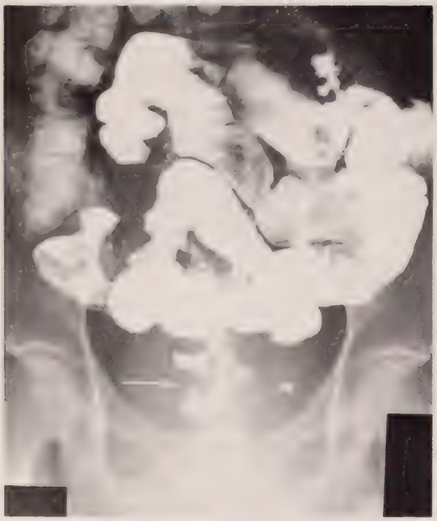


Fig. 2. Upper left Barium-enema x-ray of a 35-year-old woman with ileitis. Extrinsic pressure on lateral aspect of rectum by inflammatory mass. Barium fills loops of ileum via multiple fistulas connecting ileitis to rectum (arrows). Barium has entered left colon but not right. Colon shows retained stool despite vigorous cleansing preparation. **Upper right** Later barium-enema x-ray of same patient; multiple ileorectal fistulas are now better developed. Fistulas arise from ileum and point toward a pelvic mass (arrow); rectum is narrowed and folds are effaced. Extrinsic pressure on lateral aspect of rectum due to inflammatory mass is again seen. **Left** Still later small-bowel x-ray of same patient. Barium also fills the rectal segment without demonstrating involved small bowel. Only right colon is demonstrated. Loops of ileum proximal to zone of ileitis are dilated. Multiple pararectal fistulas (arrows). Perirectal and labial fistulas have developed, some serving to complete triple fistula tracts (ileum to rectum to perineum).

the barium enema probably reverses the pressure gradient, making this procedure successful as well. In a small percentage of cases, the fistula will not be demonstrated by either of the two procedures. In these cases, presumptive evidence of its presence will be found, often including a lower abdominal mass, lack of reflux of barium into the terminal ileum (on barium enema x-ray examination), extrinsic pressure on the sigmoid or rectum, or segmental intrinsic narrowing of one of these areas. The fistula is usually then demonstrated at a later date when it is better developed. The presence of other fistulas arising from the ileum provides supportive evidence to confirm the presence of a suspected ileorectal and ileosigmoidal fistula.

It is common for the small bowel to be chronically dilated when the fistula is present. In some cases, air fluid levels are consistently seen on plain films of the abdomen. This is best explained by the stricturing of the ileum, which tends to give rise to both the chronic obstruction and the development of the fistula. The inflammatory mass surrounding the fistula, however, might in itself be responsible for the obstruction, or contribute to it. The explanation for attacks of acute small-bowel obstruction is similar.

In some instances of fistula, the colon is atonic and chronically dilated. This, no doubt, is best explained by the extrinsic pressure of the inflammatory mass which accompanies the fistula on the rectum.

Symptoms. Symptoms directly attributable to

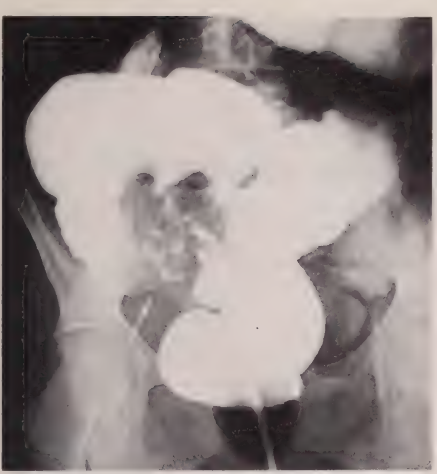


Fig. 3. Barium-enema x-ray of a 36-year-old woman with longstanding ileocolitis. Barium outlines multiple fistulas which enter involved loops of ileum via rectum (arrow).

fistula are difficult to document. A clinical-radiologic correlation has been reported for the colonic-duodenal fistula in Crohn's disease (8) but not for the ileosigmoidal or ileorectal fistula (3). This is understandable, since manifestations of the fistula usually parallel those of the primary Crohn's disease activity. Furthermore, again coincident with disease activity and its response to drug therapy, the lumen of the ileum involved with ileitis will narrow and widen and then the inflammatory mass associated with the fistula will become larger and smaller. As a result, symptoms related to the fistula will be subject to change over short periods of time.

Based on this study, however, diarrhea is not a symptom which can be identified with the fistula. On the contrary, constipation is far more common; even more common is constipation alternating with diarrhea. It is true, as Marshak frequently pointed out, that a recent or recurrent onset of diarrhea is accompanied by coincident relief of symptoms (nausea, vomiting, abdominal pain) due to the ileal obstruction, along with reduction in size of an abdominal mass. But, paradoxically, this situation is a poor prognostic sign, heralding a worsening of the primary disease process. Elimination of diarrhea with development of constipation, or at least constipation alternating with diarrhea, signifies improvement in the primary disease and closing off of the fistula, particularly if there is no coincident recurrence or enlargement of a lower abdominal mass. In almost all instances of improvement in the state of the ileitis or ileocolitis in this study, the alteration of symptoms specifically related to the ileorectal or ileosigmoidal fistula could best be cor-

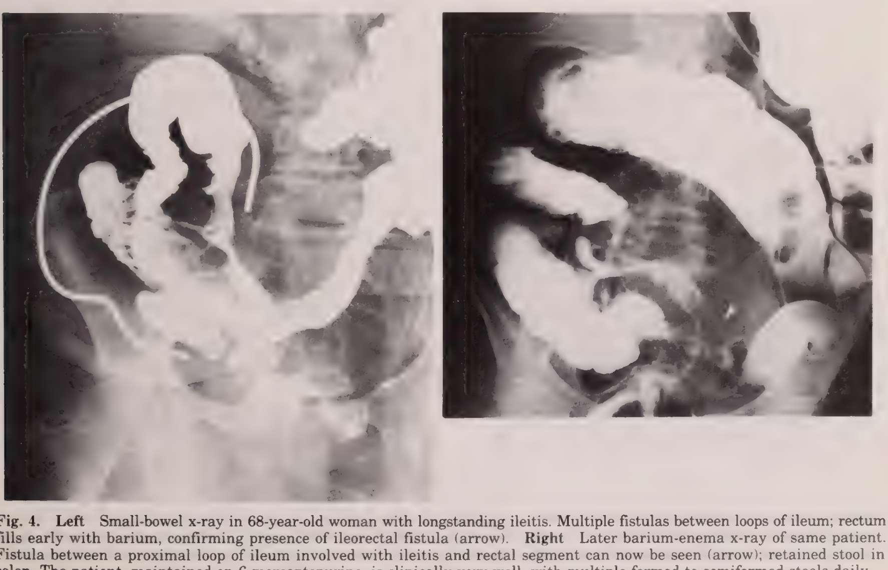


Fig. 4. Left Small-bowel x-ray in 68-year-old woman with longstanding ileitis. Multiple fistulas between loops of ileum; rectum fills early with barium, confirming presence of ileorectal fistula (arrow). **Right** Later barium-enema x-ray of same patient. Fistula between a proximal loop of ileum involved with ileitis and rectal segment can now be seen (arrow); retained stool in colon. The patient, maintained on 6-mercaptopurine, is clinically very well, with multiple formed to semiformed stools daily.

related with a favorable response to treatment with 6-mercaptopurine, as has been the case with response to other Crohn's disease fistulas (9).

Seven of the 22 patients have required ileocolic resections for progressive destruction due to Crohn's disease. In 5 of the 7, drug therapy was not satisfactory, while in 2, surgery was performed electively after drug therapy had accomplished its limited goal. In no instances did the ileorectal or ileosigmoidal fistula serve as the indication for surgery. Others, too, have concluded that the entero-enteric fistula does not require surgical intervention for its own sake (10, 11). An additional 7 patients who have been closely followed remain clinically well on maintenance drug therapy.

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Diagnosis of Extrinsic Abscesses Affecting the Small Intestine

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Abdominal abscesses or phlegmons of a variety of etiologies can develop in close relationship to the small intestine. Among the possible causes are appendicitis, pelvic inflammatory disease, diverticulitis, and amebic or tuberculous infections; these abscesses can complicate abdominal surgery, radiation therapy, and abdominal trauma. Although inflammatory processes that originate primarily in the small bowel are not part of this presentation, there are infrequent instances in which Crohn's disease in one part of the bowel produces nonspecific inflammatory changes in an adjacent small-bowel segment, and examples of this are included. In fact, it was Marshak (1) who brought this form of presentation of Crohn's disease to the attention of radiologists.

Methods

We have analyzed the barium small-bowel studies of 20 patients in whom an inflammatory process of extrinsic origin involved a segment of small bowel. All patients were studied by an intubation method, in most instances, a small-bowel barium enema, with double contrast produced by methyl cellulose (2); a single-contrast enteroclysis (3) was done in the other patients.

Radiographic Features. Displacement and compression of the small-bowel lumen are seen when the extrinsic inflammatory mass and the affected segment are shown in an oblique or lateral view. When projected en face, the same effect presents as flattening of the lumen.

Mucosal-fold thickening, presumably due to edema secondary to the adjacent inflammatory process, is a typical feature and may affect only the side of the bowel which faces the lesion. The mucosal folds are uninterrupted, and no additional mucosal alterations such as nodularity or ulceration are visible.

Fixation to the inflammatory mass may occur with long-standing lesions.

Features observed infrequently include a fistulous communication from the inflammatory process to the small bowel and partial small-bowel obstruction.

Though the radiographic changes in the affected small-bowel segment are entirely nonspecific, location and associated features related to the site of origin will usually indicate the etiology of the adjacent inflammatory process.

Results

Eleven of the 20 cases had an appendicitis-related abscess and presented the features of compression and displacement of the lumen of the terminal ileum, with thickening of its mucosal folds

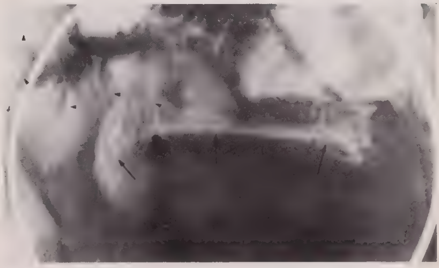

Fig. 1. Man, age 21, presented with diarrhea and pyrexia, believed due to Crohn's disease. View of enteroclysis shows compression deformity and fold thickening (arrows) caused by abscess involving terminal ileum (arrowheads) below level of cecal pole. Surgery for appendix abscess done two days later.

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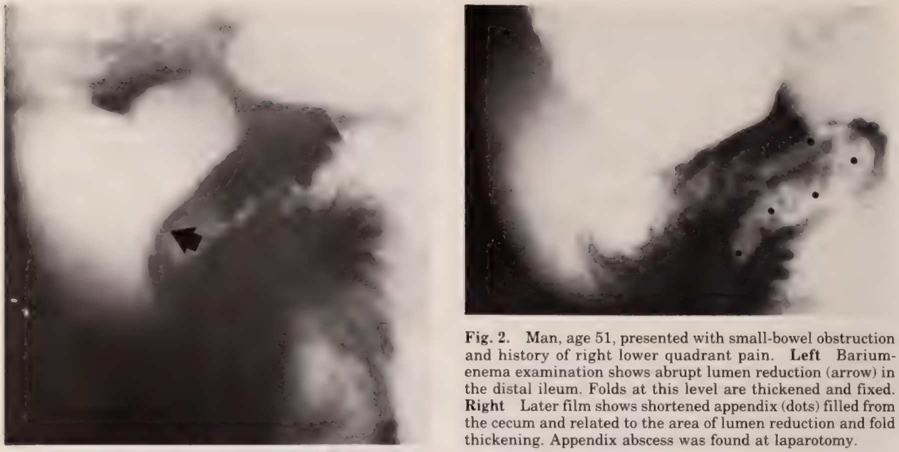


Fig. 2. Man, age 51, presented with small-bowel obstruction and history of right lower quadrant pain. **Left** Barium-enema examination shows abrupt lumen reduction (arrow) in the distal ileum. Folds at this level are thickened and fixed. **Right** Later film shows shortened appendix (dots) filled from the cecum and related to the area of lumen reduction and fold thickening. Appendix abscess was found at laparotomy.

(Fig. 1). There was similar involvement of the cecum in all but one patient. The appendix did not outline with barium in 9 of the 11 cases, but could be partly filled in 2 cases (Fig. 2). In one of the patients, a fistulous communication had formed between the abscess cavity and the adjacent ileum, and part of the appendix could be demonstrated (Fig. 3). Partial small-bowel obstruction was part of the presentation in 3 patients.

In one patient, an abscess secondary to a tuberculous salpingitis on the right side involved the cecum and terminal ileum with effects indistinguishable from those produced by an appendix abscess. In another case, pronounced lumen compression and fold thickening were caused by an infected enteric cyst of the mid-ileum (Fig. 4). Also demonstrated in individual patients were abscess formation in an area of radiation enteritis; an infected, sealed-off ventriculo-peritoneal shunt seroma (Fig. 5); and a left salpingo-ovarian abscess involving the distal ileum. There were two cases of abscess formation complicating recent surgery (Fig. 6).

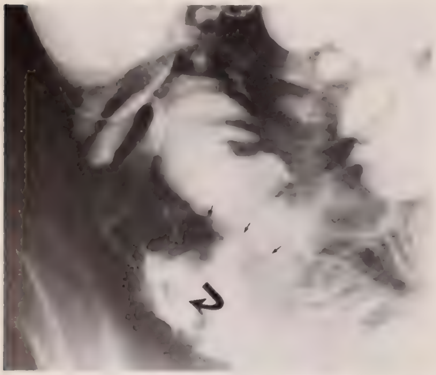
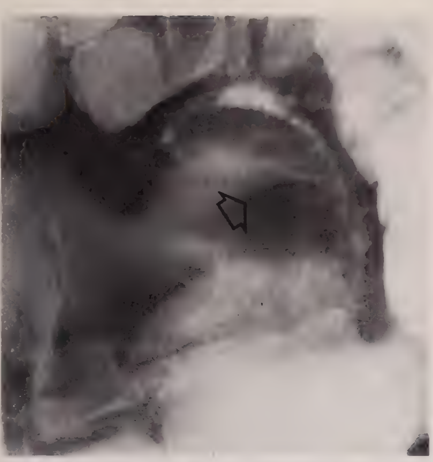


Fig. 3. Woman, age 60, admitted with tender right iliac fossa mass. Late film from small-bowel barium enema reveals abscess deforming the terminal ileum (arrows). Appendix is filled through cecum and communicates with abscess through narrow channel. An appendicolith was found at laparotomy in upper portion of abscess cavity (curved arrow).

In two patients with Crohn's disease, localized to the terminal ileum in one and to the descending colon in the other, fistula formation had occurred to an adjacent segment of small bowel. These segments presented the described, nonspecific features due to a nearby inflammatory process, did not demonstrate nodulation or ulceration, and were not involved by Crohn's disease as confirmed by postsurgical histology (Fig. 7).

Discussion

Compression, displacement, fold thickening and the absence of other alterations of the mucosa were the diagnostic features shared by all 20 cases, whatever the etiology of the underlying inflammatory process. The lumen distention effect produced by intubation methods in small-bowel examination made it possible to evaluate mucosal detail even in the presence of compression of the lumen. A variety of other noninflammatory pathologies can present with compression and displacement, among them benign and malignant



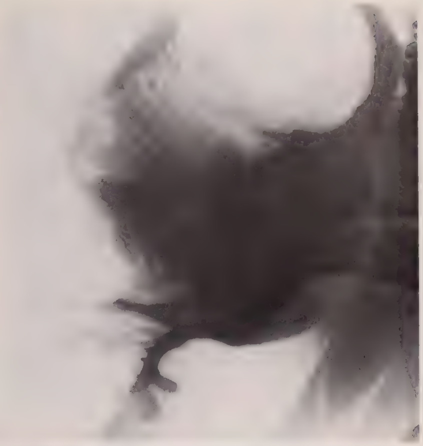
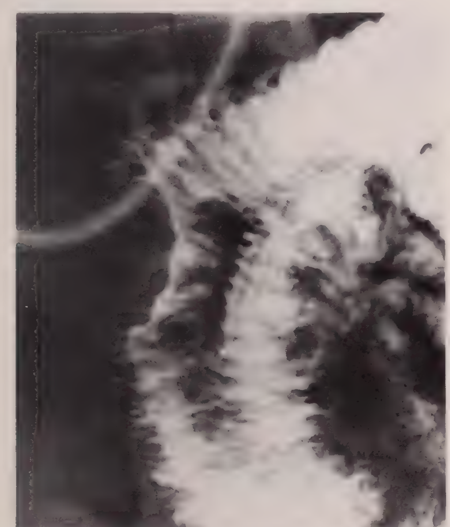


Fig. 4. Left Man, age 31, acute abdominal pain, tender mass and partial small-bowel obstruction. Small-bowel enema examination showed pronounced lumen deformity in relation to a mass lesion; compressed mucosal folds are thickened. At laparotomy, an ileum-related abscess was found. within it a small enteric cyst lined with gastric mucosa.

Fig. 5. Right Woman, age 20, ventriculo-peritoneal shunt for hydrocephalus. Exquisitely tender swelling developed in left abdomen; patient became pyrexial. Small-bowel enema examination shows localized flattening of lumen and mild fold thickening in relation to end of shunt tube and to a mass which also deforms descending colon. An infected, sealed-off seroma was later evacuated.

tumors and extensive adhesions. By purely radiologic criteria, extensive adhesions can cause particular difficulties in making a differential diagnosis. However, the absence of fold thickening and the demonstration of thornlike protrusions on compression films, as described by Sellink and Miller (5), will aid identification (Fig. 8).



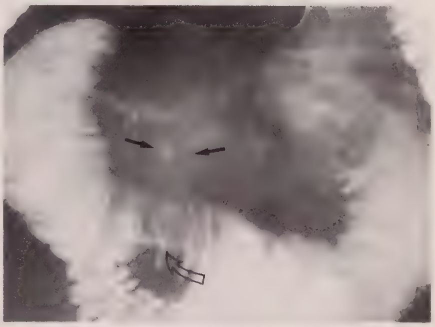


Fig. 6. Woman, age 28. History of severe endometriosis. Total abdominal hysterectomy and small-bowel resection with a re-anastomosis two weeks before. Readmitted pyrexial with abdominal pain. Small-bowel enema through decompression tube showed appearance consistent with abscess closely related to loop of ileum. Presence of a 6 cm × 6 cm abscess was confirmed by CT. Patient responded to antibiotic treatment.

Fig. 7. Woman, age 78. Recurrence of Crohn's disease after right hemicolectomy and resection of terminal ileum. Active disease is shown in neoterminal ileum with linear ulcers and lumen narrowing. Several fistulae (arrows) lead to adjacent segment of ileum which exhibits nonspecific fold thickening (open arrow). At laparotomy it was shown to be free of Crohn's disease.

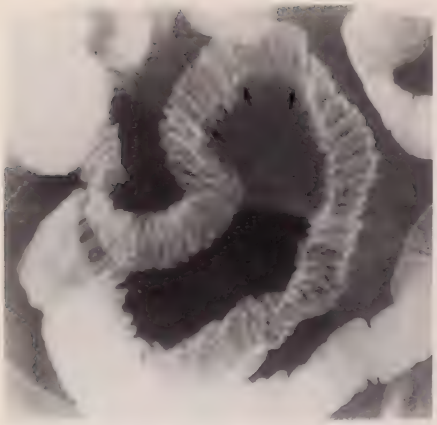


Fig. 8. Woman, age 57, with history of gynecologic surgery, presented with intermittent abdominal pain. A loop of distal ileum is fixed into a wide curve; during abdominal compression, thornlike protrusions (arrows) appear between folds of normal thickness. Only extensive adhesions were found at later laparotomy.

Most of the radiologic reports on appendicitis-related abscesses have dealt with plain-film findings or barium-enema studies. Marshak (4) has fully described the displacement of the terminal ileum, usually associated with appendicitis. Sellink (5) uses the term "appendicular infiltrate" to indicate all inflammatory processes infiltrating into the bowel in the appendix region, whether due to appendicitis, an inflamed Meckel's diverticulum, or amebiasis. Among our cases, the effects of a tuberculous abscess of the right Fallopian tube could not be distinguished from those of an appendix abscess. Of interest is the appendicoileal fistula found in one of our patients (Fig. 3). This is reported to be the least common form of appendico-enteric fistula (6). Though the rupture of an appendix abscess into a hollow viscus is not considered unusual, its persistence as a fistula is a rarity and believed to be related to the retention of an appendicolith that would prevent its spontaneous closure (7). In fact, the presence of an appendicolith was confirmed at laparotomy in the case reported here (Fig. 3).

When describing ways in which the colon can become involved in a granulomatous process, Marshak (1) included the following observation: "The colon may be involved directly by fistula formation from an adjacent loop of diseased small bowel. Such fistulas . . . do not lead to granulomatous colitis." Surgical experience, especially with regard to ileosigmoid fistulae, is in agreement with this observation. Block and Schraut (8) consider it a rarity for the sigmoid colon to be involved by true Crohn's disease when an ileosigmoid fistula exists. In 40 of their 44 patients, they were able to confine successful surgery to the resection of the diseased ileum and to local excision of the fistula with closure of the sigmoid colon. A similar experience has recently been reported in the case of entero-enteric fistulae in Crohn's disease (9). The aim of the authors of that report was to resect the smallest possible length of bowel. They removed matted loops en bloc, including the fistula. They found that fistulae usually communicated with an adherent loop of otherwise normal bowel that was tethered to the active disease process. Unless actual mucosal ulceration and thickening were discovered in relation to the fistula, its point of entry was simply oversewn.

As far as we could ascertain, no radiologic findings have yet been reported that contribute to the preoperative differentiation between actual Crohn's disease or mere nonspecific inflammatory change in relation to the entry site of an entero-enteric or colo-enteric fistula. Our case example (Fig. 7) may therefore be of interest and may serve to extend to the small bowel Marshak's observation on the effect and significance of enterocolic fistulae in Crohn's disease.

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Gastrointestinal Carcinoid Tumors: An Analysis of 104 Cases

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Abstract

We studied retrospectively 104 nonappendiceal gastrointestinal carcinoid tumors, emphasizing the various roentgenographic features caused by both primary and metastatic disease. Included are barium examinations demonstrating changes due to primary and metastatic disease. The angiographic appearance of mesenteric metastatic disease is presented, including one case showing a sunburst pattern in hepatic metastases. Computerized tomography demonstrated hepatic and nodal metastases in several cases, and in one case bowel-wall changes were seen secondary to mesenteric metastatic disease. In two cases, superior mesenteric artery ischemia with subsequent infarction led to the patients' death. A case of islet-cell carcinoid tumor in ectopic pancreatic tissue in the duodenum is reviewed.

Carcinoid tumors arise from cellular elements that originate in the ectodermal component of the fourth germ layer, referred to as the "neural crest." These cells belong to a group identified as amine-precursor-uptake-decarboxylase, or APUD, cells (1). Thus, carcinoid tumors may originate at any site where APUD cells are located, including the gastrointestinal tract, the pancreatic and biliary tracts, respiratory tract, genitourinary tract, and thymus (2).

Interest in carcinoid tumors has increased with the recognition of their ability to produce various amine and polypeptide hormones. This interest is also due to the availability of more sensitive modalities for detecting metastatic disease, namely, angiography and computerized tomography.

The appendix is the most frequent site of primary gastrointestinal carcinoid tumor. These tumors are usually asymptomatic, remain localized, and are often discovered incidentally at appendectomy. Appendiceal carcinoids were excluded from our series, but it is of interest that one case reviewed did demonstrate, by computerized tomography, evidence of mesenteric metastatic disease.

Preoperative diagnosis of gastrointestinal carcinoid tumors remains difficult due to the relative infrequency of symptoms, the small size of the primary tumor, and the variable radiographic appearance of the primary tumor, the appearance depending on the segment of gastrointestinal tract involved and the tumor morphology.

This report will emphasize the radiographic features of nonappendiceal carcinoid tumors, including manifestations of metastatic disease. Our findings will be correlated with those described in the literature.

Methods

Our series was obtained from a retrospective analysis of 104 proven cases of gastrointestinal carcinoid tumors from the Departments of Radiology of Emory University School of Medicine, the M. D. Anderson Hospital and Tumor Institute, the Medical College of Wisconsin, and the University of Texas at Dallas.

Most cases were not diagnosed preoperatively, and the majority did not demonstrate radiographic evidence of the primary tumor.

The average age of the patients in this series was 53.5 years (Table). The patients consisted of 61 men and 43 women; therefore, a slight male predominance is evident when all sites of primary

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TABLE
Gastrointestinal Carcinoid Tumors
(104 cases)

Site of primary tumor	No. cases	Age avg. yrs.	Sex	Liver mets	Nodal or mesenteric mets	Other mets	Carcinoid syndrome
Ileum*	52	56	32M 20F	29 (56%)	15 (29%)	3 (6%)	18 (35%)
Colon	22	54	15M 7F	7 (32%)	2 (9%)	2 (9%)	2 (9%)
Stomach	10	52	4M 6F	1 (10%)	1 (10%)	none	1 (10%)
Duodenum†	9	49	4M 5F	1 (11%)	1 (11%)	none	none
Unknown	7	52	4M 3F	7 (100%)	2 (29%)	2 (29%)	3 (43%)
Jejunum*	2	70	1M 1F	none	none	none	none
Pancreas	1	59	1F	none	present	none	none
Meckel's diverticulum	1	54	1M	none	none	none	none

METS, metastases.
* 18 small intestine previously reported (8).
† 6 previously reported (26).

tumor are considered. Liver metastases were documented in 45 patients. Nodal or mesenteric metastases were identified in 22 patients, and more distal metastases occurred in 7 patients. The carcinoid syndrome was diagnosed in 24 cases, the vast majority occurring in patients with one or more primary tumors in the ileum.

The most common site of primary tumor was the small intestine, which accounted for more than 50% of the cases. The next most frequent primary site was the colon, which represented approximately 21% of the total. The stomach and duodenum each comprised less than 10%. In 7 cases, the patient had metastatic disease and the site of primary tumor could not be determined.

Ileum and Jejunum. Carcinoid tumors are the most common primary neoplasm involving the small bowel (2) and, excluding the appendix, the small intestine is the most common site for primary gastrointestinal carcinoid tumors. Reports have shown the vast majority of small bowel carcinoids to be located in the ileum, primarily in its distal portion (3–5). Our series demonstrated similar findings with the primary tumor site located in the ileum or jejunum in 54 of 104 cases, and the vast majority of these tumors (in 52 of 54 cases) were located in the ileum.

The roentgenographic appearance of small-intestine carcinoids depends upon the stage of disease at the time of radiographic evaluation (2, 6, 7). Although the radiographic findings are varied, the radiographic presentations may be classified into three groups: (a) well-defined submucosal lesions (solitary or multiple); (b) mesenteric infiltration with or without associated intramural nodules; and (c) polypoid mass lesions with a mucosal based appearance (2, 4, 6–8) (Figs. 1–3).

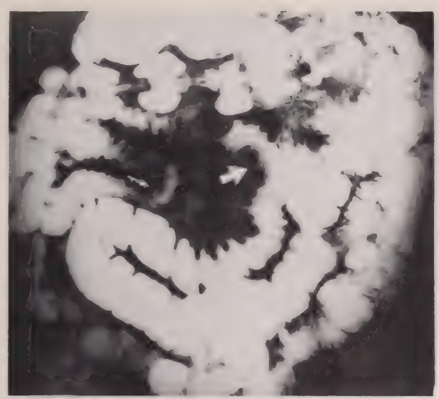
Radiographic demonstration of small solitary or multiple submucosal lesions is relatively infrequent, because the majority of the patients are asymptomatic at this stage and either do not undergo radiographic examination or the small size and lack of mucosal involvement preclude detection on barium examination of the small intestine. Findings of small-bowel obstruction, often secondary to intussusception, may be the initial finding in patients within this group. In our study, 6 patients had intussusception (Fig. 4) or small-bowel obstruction.

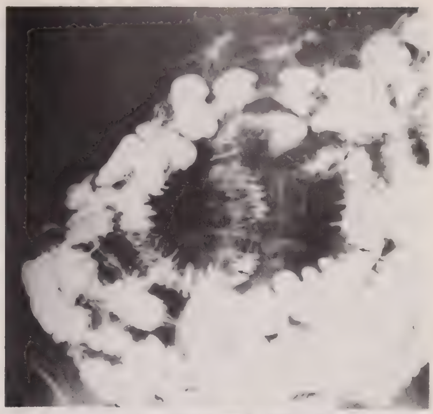
When present, mesenteric infiltration may cause kinking and angulation of bowel loops, as well as decreasing the caliber of the bowel lumen (2, 7). All of the above findings, as well as a spiculated appearance of the bowel and bowel-wall thickening, are often apparent on barium examinations. The latter two changes are frequently recognized when abdominal computerized tomography is performed (Fig. 5).

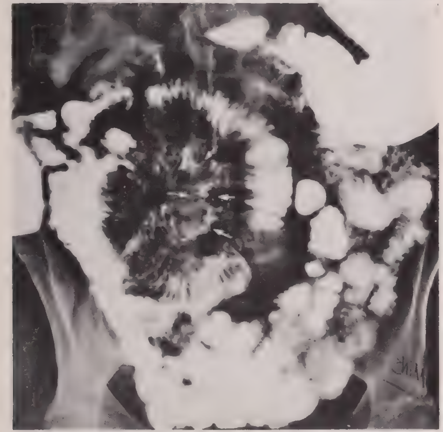
These changes are seen with other processes, such as Crohn's disease and, therefore, are not diagnostic of small-intestine carcinoids; however, such findings, when accompanied by intramural nodules, are highly suggestive of gastrointestinal carcinoid.

In some cases, submucosal lesions grow intraluminally and may present as polypoid, apparently mucosally based lesions (2). Therefore, they may be indistinguishable from mucosal lesions such as an adenocarcinoma. Unlike adenocarcinomas, however, carcinoids seldom exhibit ulceration.

Approximately one-third of small-intestine carcinoids are reported to be accompanied by metastases. When the carcinoid syndrome is present, signifying liver metastases, the primary tumors are usually in the small intestine (9). In our study, 18 of 24 patients with the carcinoid syndrome had primary tumors in the small intestine. Not all patients with liver metastases, however, develop the carcinoid syndrome. In our study, only 18 of 45 patients with hepatic metastases developed the carcinoid syndrome.







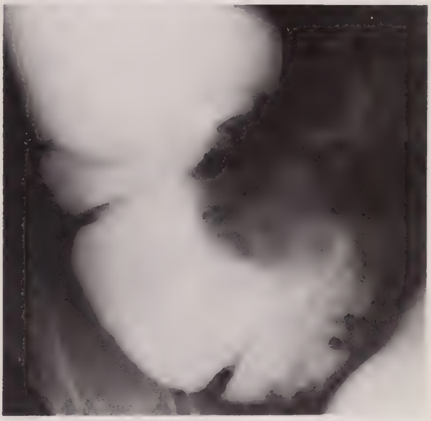


Fig. 1. Top left Small-bowel study demonstrating two intramural mass lesions of carcinoid tumor (arrows). Separation of intestinal loops by mesenteric mass effect. Associated thickening of the mucosal folds is due to muscular hypertrophy incited by tumor.

Fig. 2. Top right Multiple intramural carcinoid tumors of ileum with associated mucosal thickening and mesenteric mass effect.

Fig. 3. Bottom left Ileal carcinoid tumor. Irregular narrowing of ileal lumen secondary to tissue reaction. Displaced ileal loops demonstrate radiation of mucosal folds of inner margin toward tumor site secondary to mesenteric retraction.

Fig. 4. Bottom right Film of cecum from barium-enema examination demonstrating ileal intussusception secondary to carcinoid tumor of terminal ileum.

The ability to detect both primary and metastatic gastrointestinal carcinoid has increased with the use of angiography and computerized tomography. Angiography is useful for locating the site of a primary tumor, identified by a tumor stain (Fig. 6). Some workers report the need to use epinephrine due to a relative lack of tumor neovascularity and tumor staining related to the primary tumor (10). Angiographic evidence of mesenteric involvement is indicated by vascular irregularities, areas of vascular narrowing, corkscrew vessels, and obliteration of the distal mesenteric arcade (Fig. 7) (2, 11). The so-called "sunburst" pattern of mesenteric vessels may be absent, but with mesenteric involvement, one of the above described findings is generally present.

The majority of hepatic metastases appear hypervascular on angiography (Fig. 8). In our series, two cases demonstrated a sunburst appearance reminiscent of that seen in mesenteric metastases

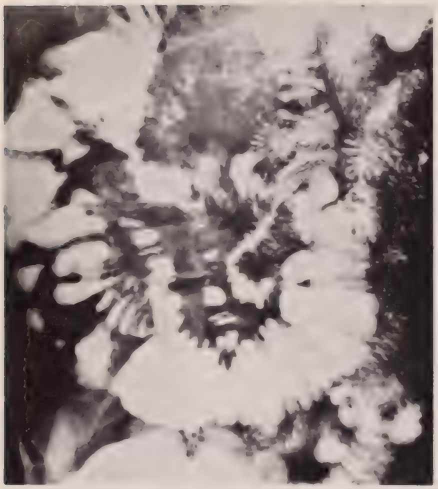
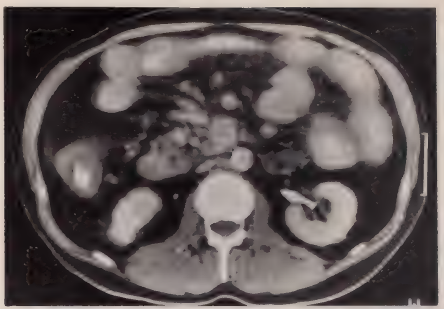



Fig. 5. **Left** Small-bowel study demonstrating thickening of bowel wall and spiculation of mucosal folds secondary to ileal carcinoid. **Right** Abdominal computerized tomography of abdomen demonstrating marked thickening of bowel wall in same patient.

(Fig. 9). However, the sunburst appearance of hepatic metastases is nonspecific and is also seen in metastatic hypernephroma and colonic carcinoma.

Computerized tomography is useful for demonstrating hepatic (Figs. 10, 11) and nodal metastases, for determining the extent of mesenteric involvement (12), and may demonstrate bowel-wall and mesenteric changes due to the desmoplastic reaction elicited by these tumors (Fig. 6).

The occurrence of distal sites of metastases in patients with carcinoid tumors has been described previously, with osteoblastic metastases in the skeleton the most frequently reported (13, 14). Three of our cases of small-intestine carcinoids exhibited distal metastases, one to bone, another to lung, and the third to the heart.

Large Bowel. The large bowel is the second most common site for primary, nonapendiceal gastrointestinal carcinoid tumors (3). Of these, the majority occur in the rectum. Rectal carcinoids account for 1%–2% of rectal polyps exceeding 0.5 cm in diameter (7). In our series, colorectal carcinoids accounted for about 21% of all cases of gastrointestinal carcinoids (22 of 104 cases). Nearly 60% of these (13 of 22 cases) were in the rectum or at the rectosigmoid junction.

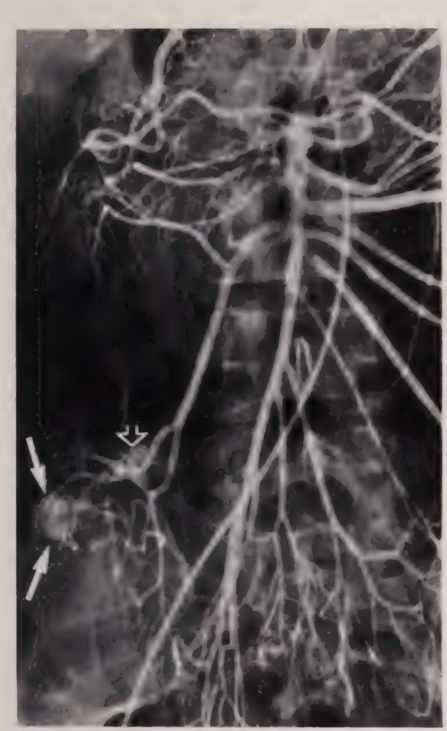
Rectum. Most rectal carcinoids are discovered incidentally during routine proctosigmoidoscopy. When identified during radiographic examination, rectal carcinoids are generally sharply marginated and broad-based (Fig. 12) (6, 7). Therefore, they are frequently mistaken for adenomatous polyps. In four of our cases, radiographic examination of the colon demonstrated sessile polypoid lesions ranging from 0.7 cm to 4.0 cm in diameter.

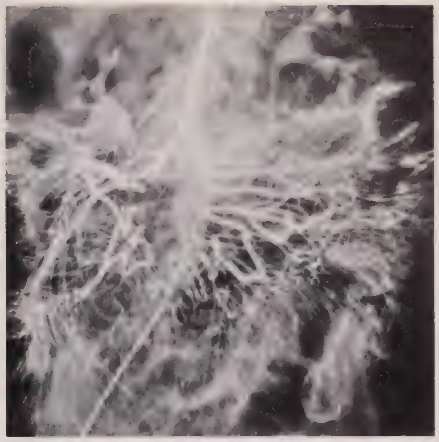
Occasionally, rectal carcinoids may have a bulky appearance and may even be annular (Fig. 13). One case in our series appeared on barium-enema examination as a bulky, almost annular rectal lesion, the appearance suggesting adenocarcinoma.

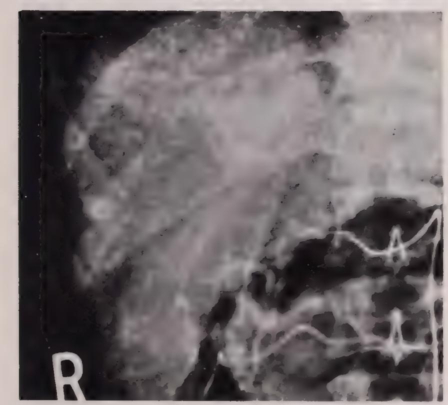
The incidence of metastases with primary carcinoids of the rectum is infrequent and reported to be as low as 10% in one series (5). However, in our series, 6 of the 13 patients (46%) developed metastases. Five patients had liver metastases, and the carcinoid syndrome was documented in one patient. The remaining patient had osteoblastic metastases.

Nonrectal Colon Carcinoids. Approximately one-third of colonic carcinoids are located at sites other than the rectum (3) (Fig. 14), and of these, about 75% occur in the right colon (15). In our series, approximately 41% (9 of 22 cases) of colonic carcinoids were located at sites other than the rectum. The percentage of cases of nonrectal colonic carcinoids occurring in the right colon (6 of 9 cases, 67%) approached that reported in the literature.

The radiographic appearance of these tumors is frequently more aggressive than those located in the rectum, because ulcerated, fungating, and "apple-core" lesions are common. It has been reported that such lesions are often indistinguishable from adenocarcinoma of the colon (2, 6, 16), and similar findings were present in our cases. Identification of a significant extramural component to the lesion has been described to be char-







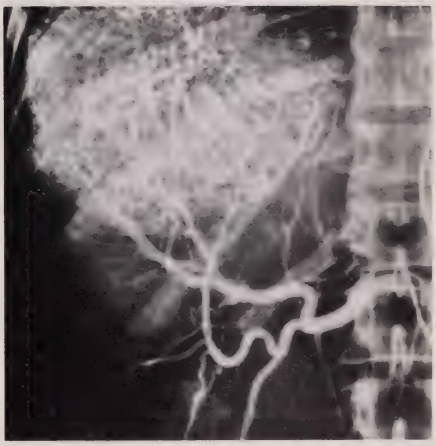


Fig. 6. Upper left Superior mesenteric artery angiogram demonstrating tumor stain (solid arrows) of ileal carcinoid. There is also tumor blush in metastatic lymph nodes (open arrow).

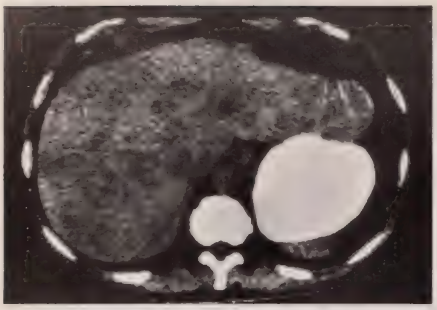
Fig. 7. Upper right Superior mesenteric artery angiogram demonstrating "sunburst" pattern of retractal response in mesentery secondary to ileal carcinoid.

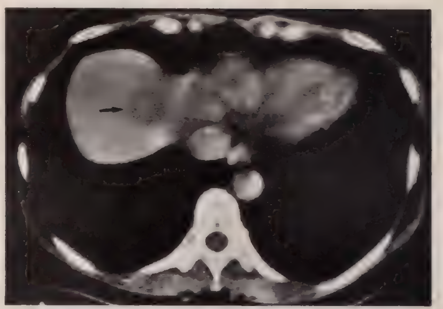
Fig. 8. Lower left Hepatic artery angiogram demonstrating multiple small hypervascular metastatic carcinoid nodules within liver.

Fig. 9. Lower right Hepatic artery angiogram demonstrating large carcinoid metastasis which is hypervascular. Vascular pattern has "sunburst" pattern similar to that seen in mesentery with carcinoid tumor.

acteristic, but nonspecific, for carcinoids of the colon (16).

The incidence of metastases from nonrectal colonic carcinoids is reported to be up to 70% (2, 6), which is significantly higher than that which occurs with rectal carcinoids. Statistics from our study revealed similar findings with 4 of the 6 patients confirmed to have metastases. Angiographic findings were similar to those seen with small-intestine carcinoids. Angiography and com-





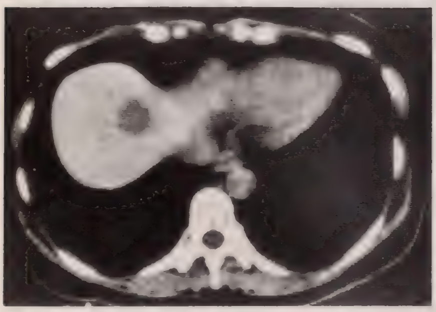


Fig. 10. Upper left Computerized tomographic scan demonstrating multiple, poorly defined metastatic focci of carcinoid scattered throughout liver.

Fig. 11. Upper right Computerized tomographic scan demonstrating solitary, poorly defined carcinoid metastasis in the liver. **Left** Repeat scan following administration of experimental liposoluble contrast agent—Ethiodized Oil Emulsion 13, which increases inherent density of normal hepatic parenchyma. Enhanced normal liver parenchyma demonstrates improved definition of carcinoid metastases.

puterized tomography are useful in identifying metastases and the extent of the disease.

Stomach. Gastric carcinoids are relatively rare and account for less than 5% of gastrointestinal carcinoid tumors (2–5, 17, 18) and 0.3% of malignant gastric tumors (3). Ten cases of gastric carcinoid tumors were identified in our study, representing almost 10% of the overall number of cases.

The radiographic appearance of gastric carcinoid tumors is variable, with approximately two-thirds reported to present as solitary tumors or, less commonly, as multiple, well-defined intramural lesions (Fig. 15) (6, 17–20). The remainder usually are polypoid intraluminal-appearing masses, indistinguishable from adenocarcinoma (Fig. 16) (6, 17, 18, 20). These tumors have also

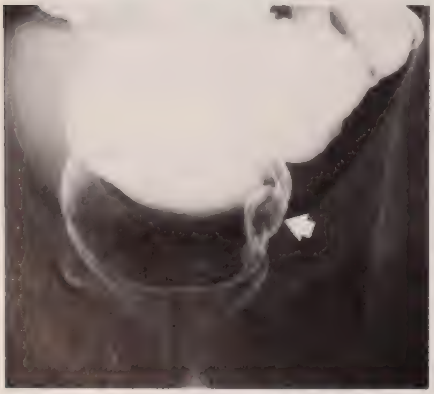


Fig. 12. Rectal carcinoid presenting as sessile polypoid lesion simulating an adenomatous polyp.

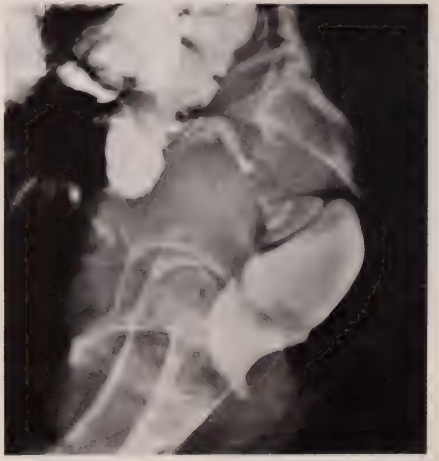
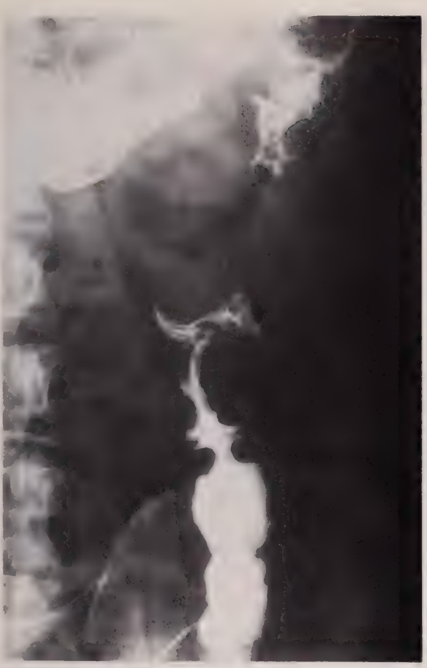
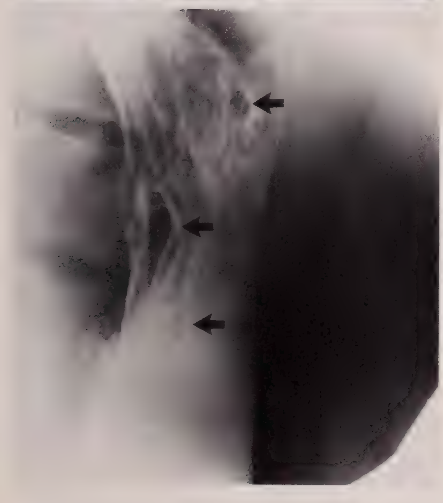
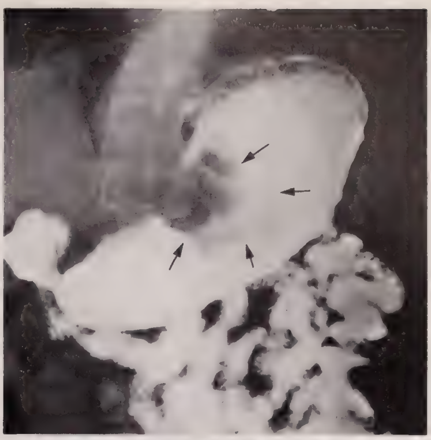


Fig. 13. Annular carcinoid tumor of rectosigmoid simulating annular carcinoma.







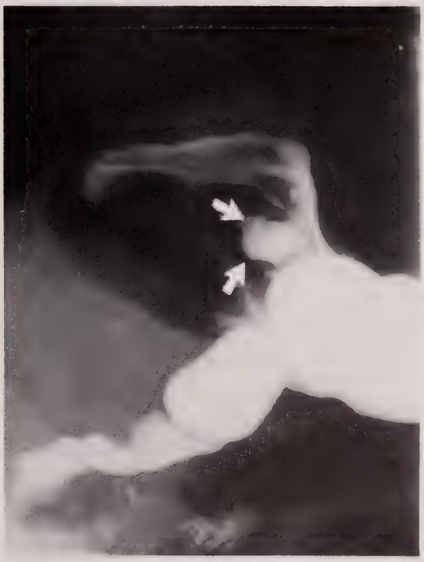


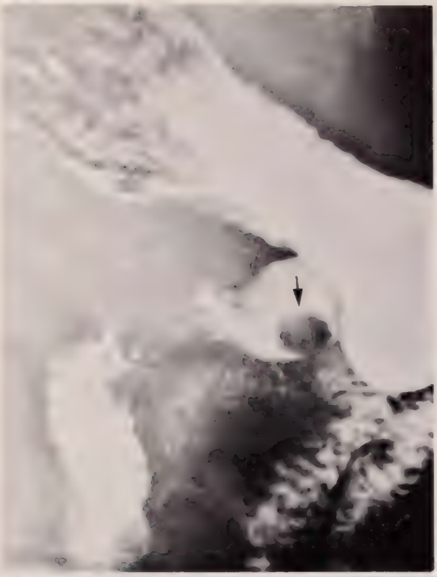
Fig. 14. Upper left Bulky carcinoid tumor involving descending colon.

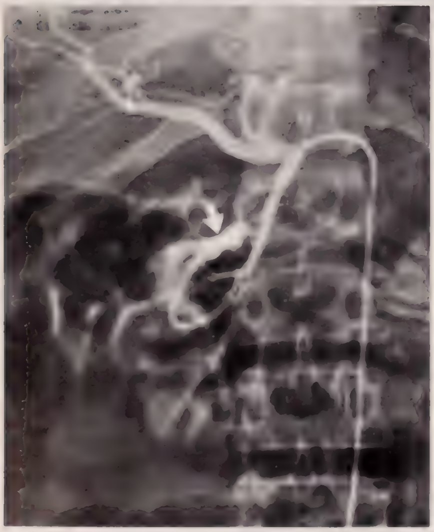
Fig. 15. Lower left Multiple carcinoid tumors of stomach presenting as intramural polypoid lesions (arrows).

Fig. 16. Upper right Large, bulky carcinoid tumor of stomach simulating polypoid carcinoma.

Fig. 17. Lower right Ulcerating carcinoid of stomach simulating peptic ulceration (arrows).

been reported to resemble large gastric ulcers (Fig. 17) with adjoining masses and multiple polyps (16, 20–22). In our series, the primary tumor was demonstrated radiographically in 50% of the cases (5 of 10 cases), and the appearance varied from a large, smoothly marginated submucosal lesion to that of a benign-appearing ulcer. The angiographic appearance of gastric





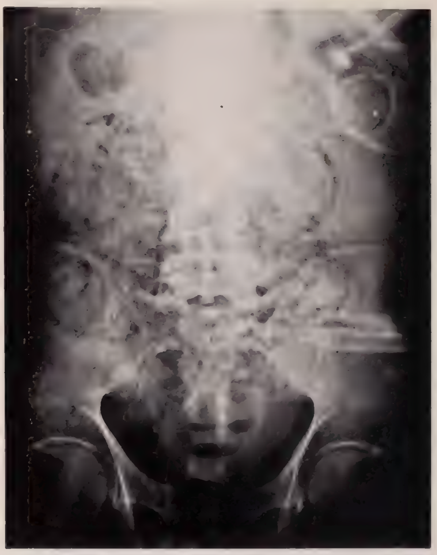


Fig. 18. **Upper left** Intramural carcinoid tumor of duodenal bulb (arrow).

Fig. 19. **Left** Selective celiac angiogram demonstrating bleeding site (arrow) from the gastroduodenal artery, caused by an ulcerating carcinoid tumor of duodenum.

Fig. 20. **Upper right** Patient with metastatic carcinoid tumor of unknown origin with compromise of superior mesenteric artery and resultant gangrene of small intestine. Pneumatosis of small intestinal loops is present.

carcinoid has been described in only one case and showed an intense tumor blush corresponding to a broad-based submucosal lesion (23).

The reported incidence of metastatic disease with gastric carcinoid ranges from 20% to 30%, and the presence of the carcinoid syndrome is rare (2, 20). In our series, metastatic disease was present in 2 of 10 cases. One case had liver metastases accompanied by the carcinoid syndrome. The other case demonstrated nodal metastases with osseous metaplasia. Unlike most other gastrointestinal carcinoids, gastric tumors are frequently associated with bleeding which may be massive (20, 24, 25).

Duodenum. The duodenum represents the primary site for gastrointestinal carcinoid tumors in 0.2%–5.4% of cases (26). In our series, duodenal tumors accounted for less than 9% of nonappendiceal gastrointestinal carcinoids.

We found that the appearance of a duodenal carcinoid may vary from that of a benign intramural lesion (Fig. 18) to that of a large, bulky ulcerating lesion. This was in accord with descriptions reported previously (26). Presentation as multiple polypoid defects within the duodenal bulb has also been described (27). One case in our series merits specific mention, an islet-cell carcinoid tumor in ectopic pancreatic tissue, located in the duodenal wall.

The incidence of metastatic disease from duodenal carcinoids is low, reported to be 25% in one series (28). In our series, metastatic disease was present in only one case. As with gastric tumors, an increased frequency of bleeding has been noted relative to other gastrointestinal sites (Fig. 19). In fact, in one case previously reported, the hemorrhage was so severe that it required embolization for conrol (26).

Unusual Sites. Two remaining tumors in our series were located in unusual sites, one in the pancreas and the other in a Meckel's diverticulum. Although rare, tumors in both of these locations have been reported previously (3).

Unknown Primary Site. Patients quite often have a metastatic carcinoid tumor (hepatic, nodal, and so on) without an identified primary tumor site (3). In our series, 7 patients (7%) had abdominal metastases without identification of the primary tumor. Hepatic metastases were present in all these cases, and 3 patients developed the carcinoid syndrome. Two of the patients had distal metastases, and 2 patients demonstrated intestinal pneumatosis due to small bowel infarction caused by superior mesenteric artery compromise from mesenteric metastases (Fig. 20). Intestinal ischemia associated with carcinoid tumors has been described in patients with ileal carcinoid tumors and is thought to be caused by changes around the mesenteric blood vessels induced by sclerosing substances released by the carcinoid tumor (29).

Summary

Carcinoid tumors occur with sufficient frequency to be included in the radiographic differential diagnosis of lesions throughout the gastrointestinal tract, with the exception of the esophagus. The increased use of newer imaging modalities has improved the ability to detect radiographic changes due to primary and metastatic carcinoid disease. Because carcinoid tumors, regardless of their site, must be considered malignant, the radiologic diagnosis should be made whenever possible, because the clinical diagnosis is often difficult due to the infrequency and nonspecificity of symptoms.

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A Pathophysiologic Approach to Nontumorous Small-Bowel Disease

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With the passing of Dr. Richard H. Marshak, medicine has lost perhaps its foremost gastrointestinal radiologist and one of its finest educators. Throughout his career, Dr. Marshak had a special interest in the small intestine. His textbook on its radiology is a classic (1). He was the author of numerous articles on malabsorption states (2–8). His work in the 1970s on immune deficiency and the small bowel is a landmark (5, 6). His refresher courses on the small bowel at meetings of the Roentgen Ray Society and Radiological Society of North America were always among the best attended. It is, therefore, fitting to dedicate to Dr. Marshak a simple scheme to aid in the diagnosis of nontumorous small-bowel disease. We hope that this scheme may be a starting point for some people, promoting understanding of pathophysiology and obviating the need for rote memorization.

The small bowel poses difficulties for most radiologists for many reasons. It is a remarkably healthy organ, and, in spite of its length and the rapid turnover of its mucosal surface, primary small bowel disease is relatively rare. Except for Crohn's disease and lymphoma, radiologists do not develop sufficient experience with small-bowel entities to permit easy recognition. In fact, none of these diseases has a truly pathognomonic appearance. The popular "Aunt Minnie" approach to diagnosis—recognizing a specific familiar pattern—is clearly impossible. Algorithms are helpful to organize an approach, but most require memorization of overlapping lists of diseases to match nonspecific patterns (9).

By appreciating the pathophysiologic mechanisms causing changes in the small intestine, and by learning the fascinating pathophysiology and natural history of the individual diseases, one can match a reasonable differential diagnosis to a given pattern without reliance on rote memorization. This is the essence of what Col. William L. Thompson, the founder of the Registry of Radiologic Pathology at the Armed Forces Institute of Pathology, termed "triangulation": the correlation of roentgen signs with pathophysiology and clinical data to arrive at a diagnosis.

Basic Roentgen Signs. Dilatation, increased fluid, prominence of folds, and nodularity of folds are the most important basic signs of small-bowel disease.

Dilatation seldom occurs alone and is generally best judged subjectively rather than measured.

Increased fluid in the bowel is reflected by dilution of the barium column causing blurring and haziness of its outline. Increased fluid also affects coating and may lead to fragmentation, flocculation, and layering of barium within the intestinal loops; these are less specific signs, being dependent more upon types of barium mixtures than on bowel fluid. Segmentation of barium into larger clumps is also seen in the presence of increased fluid, but is more often an effect of segmental motility disturbances and atony in states such as celiac sprue.

Prominence of folds is the most important small-bowel roentgen abnormality and often is combined with the above secondary signs.

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Nodularity is occasionally superimposed upon thick folds but may be seen alone.

The Normal Fold. Normal small-bowel folds are fixed, crescentic bands of mucosa supported by a core of fibrovascular submucosa. They start to appear in the second part of the duodenum and become most prominent in the jejunum. Jejunal folds are normally 1–2 mm wide and 5–6 mm tall; they are spaced a few millimeters apart, becoming lower and farther apart in the ileum. The mucosa covering the folds is villous columnar epithelium consisting of mucus-producing and absorptive cells over loose connective tissue, the lamina propria (Fig. 1). The mucosa is separated from the submucosa by the muscularis mucosae. While major vascular and lymphatic channels run in the submucosa, tiny capillaries extend into the villi. The villi are usually just at our limits of roentgen resolution unless they are pathologically enlarged (10). Lymphoid follicles are scattered throughout the small bowel, often bridging the muscularis mucosae, appearing to be either mucosal or submucosal. They are generally hidden within the structure of the villi and folds, and are not detected radiographically unless they are enlarged.

Enlargement of any of these structures (the supporting wall, the normally very thin fibrovascular submucosal core of the fold, or the mucosa) may cause enlargement of folds roentgenographically (11) (Fig. 2). Gross distension of the villi tends to give a grainy, punctate, or shaggy appearance associated with diseases such as lymphangiectasia or Whipple's disease.

Diagnosis

Exclusion of Look-Alikes

Before considering the many rare causes of thickened small-bowel folds, it is prudent to exclude those common entities which may produce similar morphologic changes.

Edema creates a classic pattern of diffusely enlarged folds. Increased interstitial fluid affects all layers of the bowel wall, but especially and uniformly increases the volume of the submucosal space and its extension into the cores of the folds. The result is thickening of the bowel wall, stiffening of loops of bowel, and diffuse and uniform thickening of the folds. Edema, of course, is not a distinct disease. Suspicion of its presence should prompt a search for its etiology. Common causes include fluid overload (either natural or iatrogenic), increased venous pressure (usually from heart failure or portal hypertension), and decreased oncotic pressure (as in hypoproteinemia from renal failure or cirrhosis) (Fig. 3). Since edema is a systemic effect, the entire bowel is usually involved and, in some cases, the stomach and colon are affected as well. Occasionally, edema may be localized to a single loop or region, as in obstruction of mesenteric veins or lymphatics by metastasis.

Crohn's disease is one of the most common mal-

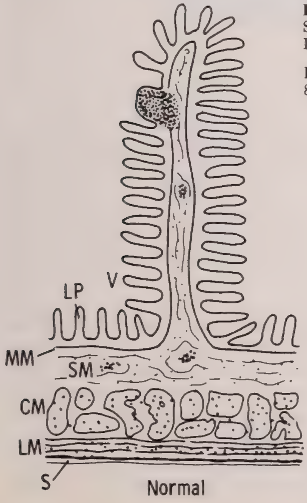


Fig. 1. Left Normal fold. V, villus; LP, lamina propria; MM, muscularis mucosae; SM, submucosa; CM, circular muscle; LM, longitudinal muscle; S, serosa. Armed Forces Institute of Pathology Neg. 83-9512.

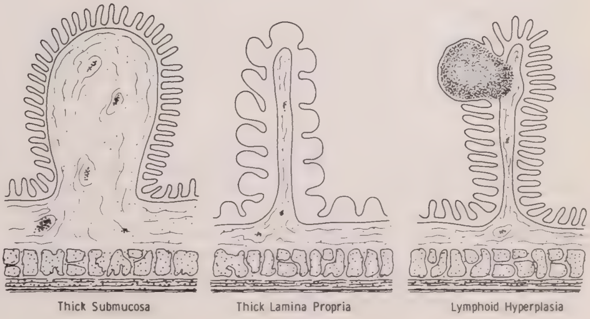
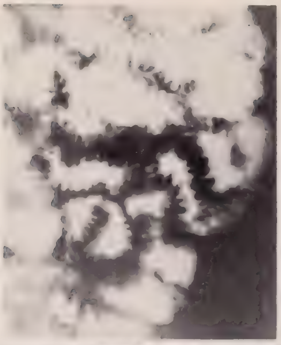
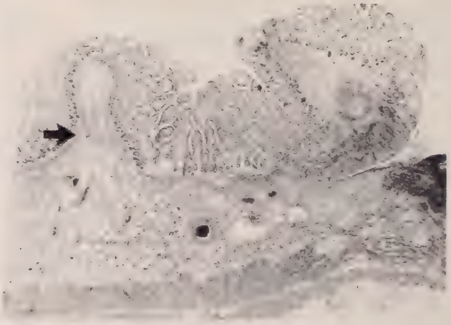


Fig. 2. Right Examples of enlarged folds. Armed Forces Institute of Pathology Neg. 83-9512.





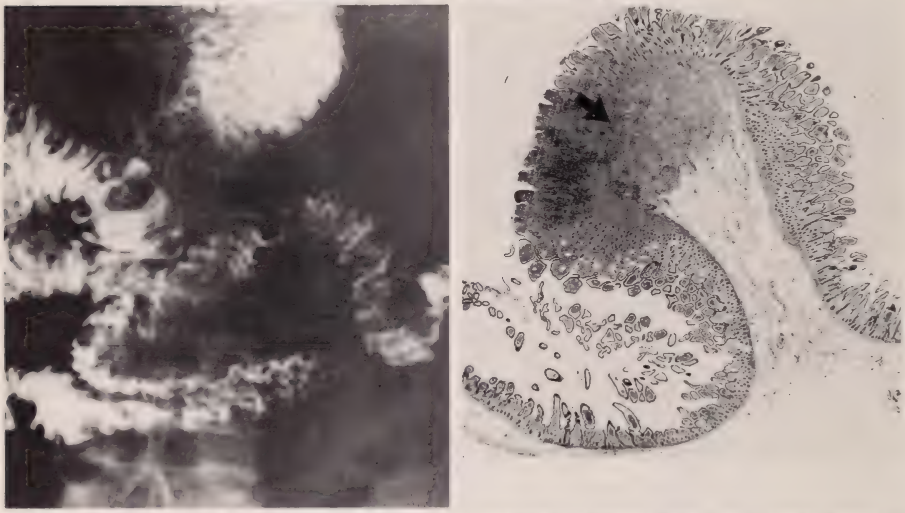


Fig. 3. **Upper left** Nephrotic syndrome frequently causes thick folds because of associated edema. Armed Forces Institute of Pathology Neg. 70-12081.

Fig. 4. **Upper right** The large folds seen occasionally in Crohn's disease are caused by infiltration of mucosa and deeper structures with inflammatory cells and granulomas. Note thickened submucosal space which extends up into fibrovascular core of fold (arrow) (H & E 130 ×). Armed Forces Institute of Pathology Neg. 75-7713. Reprinted with permission of *American Journal of Roentgenology*.

Fig. 5. **Lower left** Nodular and thickened fold pattern is seen in this case of reticulum-cell sarcoma of small intestine. Armed Forces Institute of Pathology Neg. 69-11313. **Lower right** Thickened folds are secondary to infiltration of fibrovascular core with lymphomatous cells (arrow) (H & E 10 ×). Armed Forces Institute of Pathology Neg. 75-9689. Reprinted with permission of *American Journal of Roentgenology*.

adies in North America and Europe to affect the bowel. Every radiologist is familiar with the diversity of its effects. While fold thickening is almost never its only manifestation, some element of thickening and nodularity is very common. The thickening results from infiltration of the mucosa and deeper structures with inflammatory cells and granulomas (Fig. 4). Localized or generalized edema may be superimposed. Ulcers may isolate islands of inflamed, swollen mucosa, forming pseudopolyps which can resemble irregularly thickened folds. If the islands are larger, the classic cobblestone appearance is produced.

Lymphoma may affect the small bowel and has such diverse manifestations that it can mimic almost any pattern imaginable. A constant feature is the malignant proliferation of a population of lymphocytes. This can produce a very diffuse and uniform infiltration or a single, large, almost spherical mass. Most commonly, lymphoma causes a combination of these effects, resulting in a local or patchy thickening of the bowel wall and folds in a somewhat nodular pattern (Fig. 5). Localized aggregates in the submucosa tend to give flatter nodules resembling variably sized thumbprints, whereas accumulations of lymphocytes near the tips of folds, particularly in the mucosa, may cause a very fine, nodular pattern superimposed on more normal underlying folds.

Implementation of Pattern Approach

Having excluded edema as a cause of diffuse fold thickening and Crohn's disease and lymphoma as a source of almost any other pattern, one can proceed to match an observed morphologic change with mechanisms known to operate in other disease states.

Dilatation. The most common causes of dilatation seen in clinical practice are obstruction and adynamic ileus, and these conditions must be excluded before other primary small-bowel disease is considered. Only a few other conditions are characterized by dilatation alone without significant secondary findings. The collagen vascular diseases (particularly scleroderma) can be regarded as prototypical (12). Scleroderma produces muscular atrophy, resulting in flaccidity and dilatation. Atrophic muscle is replaced by collagen in a patchy fashion, and scarring may be related to an element of vasculitis. The intestinal folds in patients with scleroderma may be thinned by stretching but should not be widened. Local areas of sclerosis occasionally result causing an uneven distension of the bowel referred to as the "hidebound" appearance (13).

Sprue is another condition in which abnormalities of peristaltic activity lead to atonic, flaccid segments which become dilated (2). In sprue, the segmental dilatation may be transient and contribute to the common findings of intussusception and segmentation seen on barium small-bowel series.

Increased Fluid. The presence of increased fluid in the bowel is most directly demonstrated by dilution of the barium column beyond that normally seen at the leading edge. As noted above, the other classic signs of flocculation, fragmentation, and segmentation are usually artifacts of barium preparation. A number of mechanisms cause a segment of bowel to contain too much fluid. While the small bowel is properly considered an absorptive organ (handling many liters of fluid per day), on balance, it actually produces more fluid than it absorbs, by one to two liters per day, which is later absorbed by the colon. Metabolic or hormonal influences (for example, from endocrine tumors) or irritative effects, as in giardiasis, may increase bowel secretion. Interference with the absorptive function of the mucosa by obstruction of lymphatic capillaries in the villi (Whipple's disease) or by infiltration of the lamina propria (amyloidosis) may tip the balance towards increased fluid. Gross distension of lymphatic capillaries or lacteals in the villi (lymphangiectasia) may result in their rupture, causing direct loss of lymphatic fluid into the lumen. Fluid may be drawn into the bowel lumen by osmotic pressure. This is most graphically demonstrated by the dilution seen when hypertonic, water-soluble contrast material is introduced into the small bowel. Increased osmotic load is also the mechanism for increased fluid in lactose intolerance. The bowel readily absorbs simple monosaccharide sugars, but disaccharides must first be split by disaccharidase enzymes in the bowel mucosa. A deficiency of such enzymes leaves unsplit disaccharides in the lumen to act as an osmotic load. Increased fluid can also result from too much input. Such a mechanism operates with the gastric hypersecretion of Zollinger-Ellison syndrome and with the increased pancreatic secretion in the VIPoma type of islet-cell tumor.

Often one disease will cause a combination of effects. For example, in the blind-loop syndrome, bacterial overgrowth produces abnormal breakdown products of sugars and fat. This causes increased fluid by osmotic load and also by direct irritating effects. In lymphangiectasia, the direct input of lymph contributes to the fluid. Additionally, the osmotic load is increased, and abnormalities of the lymphatic system interfere with fluid absorption.

Increased fluid is frequently present in sprue and can be more striking than dilatation. Even scleroderma may have increased fluid as a secondary finding. This cannot be explained easily by the primary pathophysiology of atrophy and sclerosis, but is due to very pronounced, long-term stasis leading to a situation analagous to the blind-loop syndrome with bacterial overgrowth.

Thick Folds. Most small-bowel diseases produce at least some element of fold thickening, and a number of pathophysiologic mechanisms may be involved. The layer of bowel wall affected and the amount of bowel involved are key factors determining the radiographic appearance.

Edema produces the prototypical pattern of diffuse smooth thickening. Actually, any mechanism which gives a uniform distribution of any substance—edema fluid, blood, or a metabolic product—will produce a similar appearance. As the volume of fluid or accumulation of cells increases locally in the submucosa, the mucosal covering of adjacent folds may stretch, producing the classic sessile nodular appearance known as "thumbprinting" (Fig. 6). Bleeding ordinarily causes only a single loop to be involved. Central thumbprinting tapers gradually to minimal fold widening at the periphery. Submucosal fluid under low pressure, such as venous bleeding or exudates in ischemia, is often more obvious in the relaxed bowel, becoming effaced when the bowel wall is distended. Arterial bleeding may more nearly mimic firm cellular infiltrate.

Proteinaceous deposits seen in amyloidosis and Waldenstrom's macroglobulinemia may be diffuse and may appear as uniform thickening of folds (Fig. 7) (14). Often, however, ischemia from perivascular deposition, accumulation of material in the lamina propria, and secondary lymphangiectasia cause a bizzare appearance resembling Whipple's disease.

Primary lymphangiectasia is a congenital generalized abnormality of the lymphatic system. When the small bowel is severely involved, protein-losing enteropathy ensues. Histologically, the main defect is striking dilatation of the lymphatic vessels (Fig. 8). The variation in size and distribution of these dilated vessels causes irregular fold enlargement and even thumbprinting. Superimposed on this primary process is edema of hypoproteinemia and the luminal fluid excess caused by the mechanisms described above. Usually the entire bowel is affected to about the same degree (15).

Some diseases or conditions, such as Whipple's disease, cause nonuniform fold prominence. Whipple's disease is a rare disorder seen most often in older men. Diarrhea from small bowel malabsorption is classically preceded (often by several years) by migratory large-joint arthralgias from a nondestructive synovitis. Microscopically, there is accumulation of PAS-positive material in macrophages, mainly in the lamina propria and in mesenteric nodes with a predominantly proximal small-bowel distribution (Fig. 9) (3). In 1907, Whipple thought this was a primary lipodystrophy, because of the fatty material in the lymphatic system (16). We now know that the PAS-positive material is a product of bacterial breakdown and that antibiotics are effective treatment. An infectious agent is suspected, but no specific organism has been shown to satisfy Koch's postulates.

Nodularity. A small-bowel nodule may be formed by any discrete accumulation of material beneath the mucosal epithelium. Fluid accumulations causing pliable thumbprint patterns are a special case already considered. Larger nodules formed by cellular deposits, as in lymphoma or inflammation, also have been discussed. Gross distention of the villi may lead to a pattern of very tiny nodules almost always superimposed upon diffusely thickened folds (as in Whipple's disease or lymphangiectasia).

A commonly encountered intermediate pattern is multiple, rather uniform, small nodules of 3–5 mm diameter. If the nodules are distal and if lymphoma and Crohn's disease are excluded, benign lymphoid hyperplasia may be the cause. Lymphoid follicles occur normally and are found scattered widely throughout the bowel, predominatingly in the terminal ileum. They are tiny lymphoid aggregates with germinal centers lying submerged in the deeper layers of the mucosa adjacent to, or bridging over, the muscularis mucosae, and normally are not seen radiographically.

Production of immunoglobulins is a major function of these lymphoid structures. They may become hyperplastic in response to stress on the immune system, especially by viral infection. As these structures enlarge, they bulge the overlying epithelial layer, producing macroscopically visible, smooth-surfaced nodules. Sometimes, as the nodules grow larger, the distended overlying epithelium breaks down, producing small, central erosions or umbilications which may retain tiny flecks of barium. This appearance is typical, but

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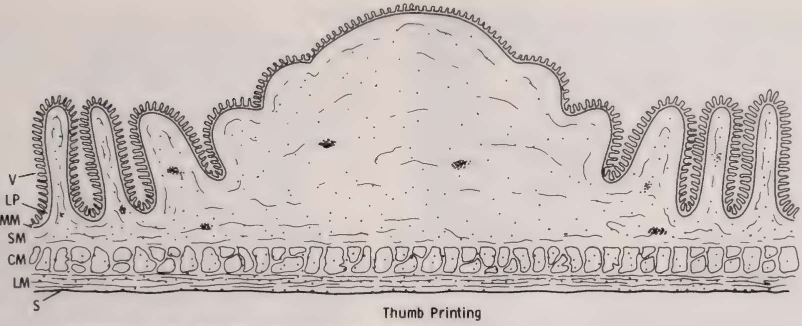
Fig. 6. **Top** Stretching of covering mucosa by underlying fluid or cells can cause the classic thumbprint. Key: See Fig. 1. Armed Forces Institute of Pathology Neg. 83-9521-2.

Fig. 7. **Middle left** Amyloid can cause uniform fold thickening diffusely. Armed Forces Institute of Pathology Neg. 69-9700. **Middle right** Proteinaceous amyloid infiltrates the submucosa and surrounds small capillaries (arrow) (H & E 50×). Armed Forces Institute of Pathology Neg. 75-9694. Reprinted with permission of *American Journal of Roentgenology*.

Fig. 8. **Bottom left** Lymphangiectasia causes diffuse fold thickening and can cause increase in fluid. Armed Forces Institute of Pathology Neg. 75-8843. Reprinted with permission of *American Journal of Roentgenology*. **Bottom right** Dilated villous and submucosa lacteals are in part responsible for thickened folds (arrow). Their rupture with spillage of contents into intestinal lumen is partly responsible for increased fluid in small bowel (H & E 80×). Armed Forces Institute of Pathology Neg. 75-9687. Reprinted with permission of *Gastrointestinal Radiology*.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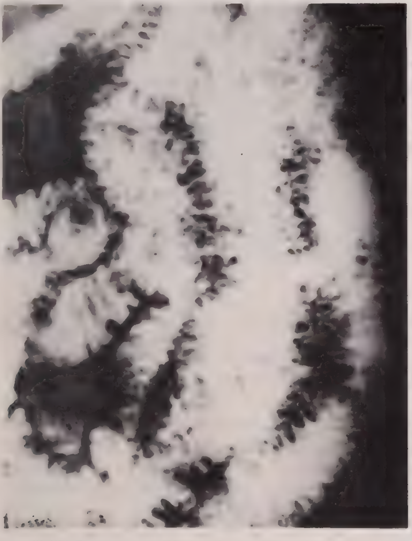

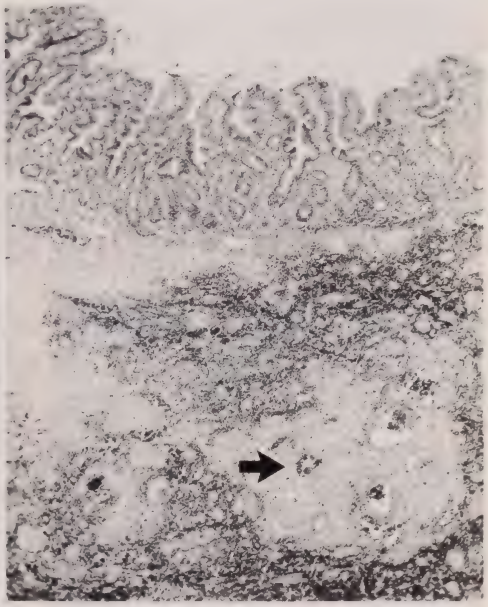

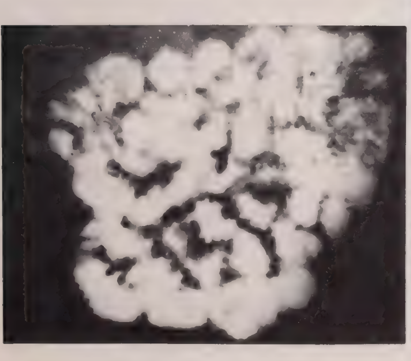

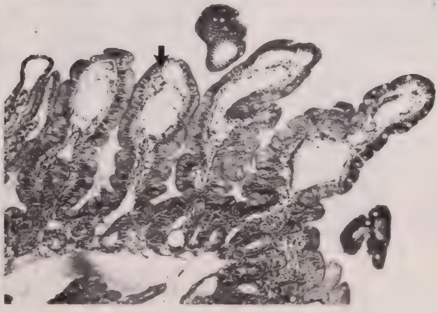

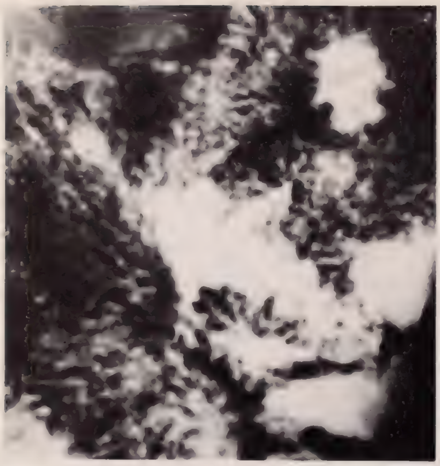

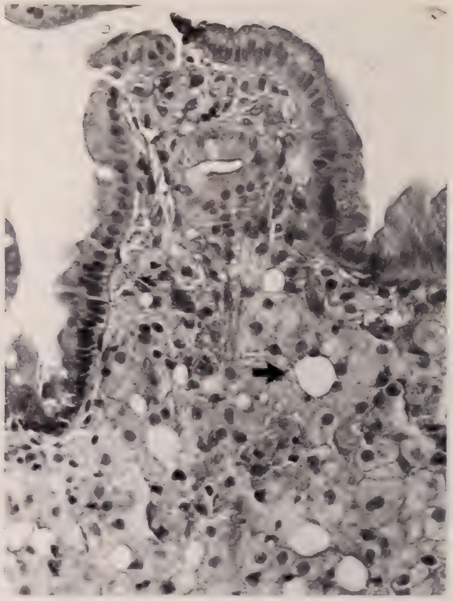

Fig. 9. **Left** Whipple's disease causes irregularly enlarged folds primarily in a jejunal distribution. Armed Forces Institute of Pathology Neg. 71-486. **Right** Fold enlargement is secondary to enlargement of lamina propria with PAS staining macrophages. Lymphangiectasia is also a prominent part of this condition in some cases (arrow) (H & E 200×). Armed Forces Institute of Pathology Neg. 75-9692.

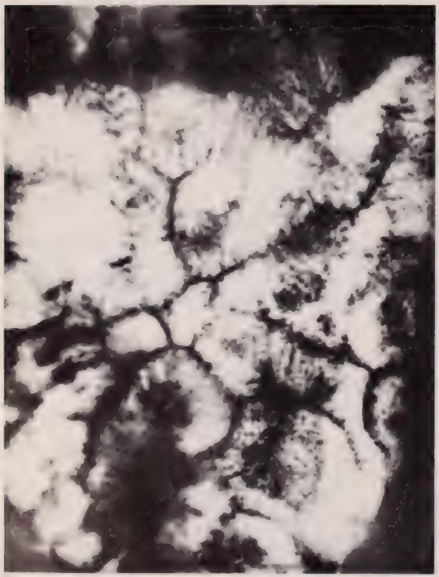

Fig. 10. Nodular lymphoid hyperplasia associated with immune deficiencies is a more proximal and diffuse condition. Note tiny nodules studding small intestine. Armed Forces Institute of Pathology Neg. 72-17035. Reprinted with permission of *American Journal of Roentgenology*.

may be seen in any process which similarly stretches the epithelium, such as lymphoma or submucosal metastasis, and is thus not specific.

Lymphoid hyperplasia, if confined to the terminal ileum and proximal colon in children and young adults with recent viral infections, is generally considered a normal variant. When more extensive or when seen in adults (who usually have less reactive lymphoid systems), a primary immunologic deficiency state must be considered (Fig. 10) (6). Lymphoid follicles become hyperplastic in response to a drive to produce plasma cells and, in turn, immunoglobulins. Profound hypoglobulinemia, especially low Ig-A, is commonly found. One must differentiate this from the discretely nodular form of lymphoma, a common association.

Summary

Examination of the abnormal small bowel evokes an extensive differential diagnosis which must take into account many uncommon entities. Variability and overlap of patterns precludes memorization of pathognomonic appearances. First, the most common entities such as edema, Crohn's disease, and lymphoma should be excluded. Then, an approach based on the correlation of roentgen findings with their underlying pathophysiologic mechanism is advocated. By determining which mechanisms may be appropriate to a given clinical pattern, one may often suggest specific diagnoses rather than recite a list of all entities which can be associated with a particular roentgen finding.

Acknowledgments

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The Value of Computed Tomography in Crohn's Disease

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Abstract

In patients with Crohn's disease, computed tomography provides extremely valuable information on masses involving the bowel and mesentery, especially as an adjunct to conventional barium studies. However, computed tomography is not the primary means of investigating Crohn's disease.

Crohn's disease is a chronic disorder of unknown etiology characterized by granulomatous inflammation involving bowel and mesentery. In Crohn's disease, transmural cellular infiltrate, edema, and later, fibrosis result in thickening of the bowel wall, often in an asymmetric fashion and involving skip areas (1–5). Fistula formation and abscesses, due to sealed off perforations, occur in 20–30% of patients with advanced Crohn's disease (1–3, 6). Diagnostic evaluation of patients with Crohn's disease is often difficult because of previous surgery and steroid therapy masking clinical symptoms.

Mucosal abnormalities (aphthous lesions, pseudopolyps, and ulcerations) are imaged only by conventional barium studies, the initial imaging modalities of choice (1, 2). Contrast studies evaluate mucosal abnormalities, but the full extent of mural, serosal, and mesenteric disease often remains obscured. The ability of computed tomography (CT) to display small density differences allows differentiation of the bowel wall from surrounding mesenteric fat (7), and thus enables evaluation of the extramucosal extent of Crohn's disease by displaying the bowel lumen, bowel wall, and mesentery (3). The value of CT in the management of 29 of our patients with known Crohn's disease is presented.

Methods. Between January 1978 and March 1983, 29 patients with known Crohn's disease were studied by CT. Indications for CT included evaluation of mass effects on bowel loops seen on conventional contrast studies or clinically suspected abscess. CT scans were obtained using a Siemens Somatom DR3 or AS&E 450 scanner. A dilute (1–2%) solution of iodinated oral contrast material (E-Z CAT, Gastrographin) was used routinely. CT findings were correlated with clinical and laboratory data, the results of barium studies, and findings at laparotomy.

Results. Of 29 patients studied, CT was thought helpful in the diagnostic workup and management of 11 patients (34%). The most common feature, seen in 10 patients on CT, was a thickened bowel wall which showed isodensity to the surrounding normal gut (Fig. 1). In evaluating the underlying cause of bowel separation on conventional studies, CT revealed abscess in three cases, fibrofatty infiltration in three cases, and diffuse, ill-defined inflammation of the mesentery in one case. CT findings of abscess formation consisted of well-marginated soft tissue mass with inhomogeneous attenuation (Fig. 2). In two patients, a fistulous tract from a diseased bowel loop extending into the adjacent liver resulted in hepatic abscess formation (Fig. 3). In one patient, perirectal inflammatory changes associated with Crohn's disease appeared on CT as nodular mass densities (Fig. 4). CT's density discrimination allowed for identification of a small amount of contrast medium in the bladder of a patient with an enterovesical fistula missed by

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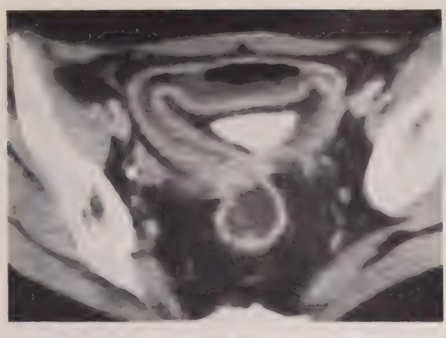
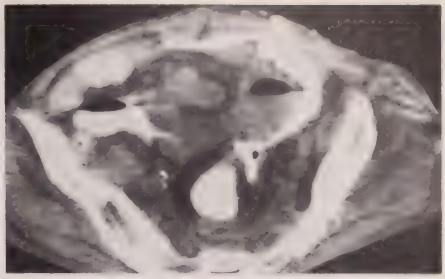
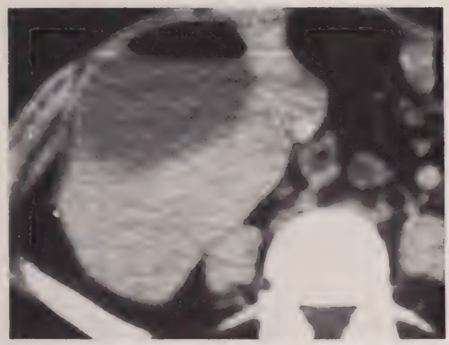






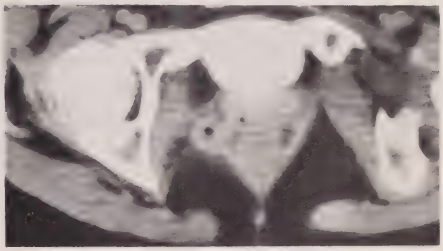


Fig. 1. Top left. Crohn's disease involving long segment of distal ileum. CT scan: wall thickening and fingerlike projections into the mesentery.

Fig. 2. Top right. Long-standing Crohn's disease of distal ileum. Markedly separated ileal loops on contrast studies. CT scan: mesenteric abscess containing gas (diagnosis proved at surgery).

Fig. 3. Bottom left. Crohn's disease with fistula extending into adjacent liver. CT scan: large, gas-containing hepatic abscess.

Fig. 4. Bottom right. CT scan: air-containing perirectal abscess associated with Crohn's disease.

conventional sinogram (Fig. 5). Carcinoma superimposed on Crohn's disease appeared as a nonspecific right lower quadrant mass (Fig. 6). Typical mucosal ulcerations in the ileum were seen on CT in only one patient (Fig. 7).

Discussion. In CT scans of patients with Crohn's disease, bowel-wall thickening (greater than 4 mm), mainly of the terminal ileum, is the most common abnormality, and has been reported in 80% of patients (3, 8). On CT scans, the thickening of the bowel wall associated with Crohn's disease is of a density equal to that of normal bowel wall (3). Occasionally, CT displays luminal narrowing and proximal dilatation similar to conventional studies (3). However, thickening of the bowel wall revealed on CT is a nonspecific finding seen with other inflammatory processes such as diverticulitis, hemorrhage, edema, and various neoplasms (3, 9–11). Both lymphoma and metastasis may affect the bowel wall primarily, rather than the mesentery (9, 11). On CT, a finding of fingerlike projections extending from the bowel wall into the mesentery may occasionally distinguish inflammatory change of Crohn's disease from neoplastic disease (9). Rarely, thickening of the bowel wall may be mimicked by a nondistended segment of normal bowel (11). Bowel-wall enhancement with intravenous contrast material is a nonspecific finding associated with Crohn's disease or ischemic colitis (11, 12).

CT demonstrates mesenteric abnormalities by identifying fluid, fat, soft tissue, air, or contrast material (9). Mesenteric fat exhibits CT attenuation values of minus 100 to minus 160 HU, with deviation from these values indicating the presence of fluid, cellular infiltrates, hemorrhage or fibrosis (3). CT findings indicating abscess formation are inhomogeneous soft tissue masses, often containing gas or contrast material (11). CT thus differentiates the proliferation of fibrofatty material and diffuse inflammatory reaction of Crohn's disease—warranting no specific therapy—from abscess formation (3). On CT for Crohn's disease involving the mesentery, one should also consider diagnoses of tuberculosis, lymphoma, and metastases. Tuberculosis may present with features very similar to Crohn's disease (8). Mesenteric metastases often appear as well defined, confluent masses ("omental cake") (13). Lymphoma characteristically may occupy a large part of the mesentery surrounding vessels and bowel loops ("sandwich sign") (14). Mesenteric adenopathy seen on CT is a nonspecific finding and may accompany fibrofatty proliferation, mesenteric abscess, and malignancies (3). CT occasionally reveals complications of Crohn's disease, such as hydronephrosis, liver abscesses, and malignancy (15–17). CT may offer a less painful alternative to barium studies to evaluate perianal and peristomal manifestation of Crohn's disease (3), and it differentiates abdominal-wall abscesses from more ill-defined cellulitis or phlegmone (18).

Barium studies, sinograms, cystograms, and methylene blue studies remain methods of first choice for the detection of fistulas (3, 7). However, CT's density discrimination may occasionally display small amounts of air or contrast material due to fistula formation not identifiable by conventional radiographic means (1–3, 7, 11).

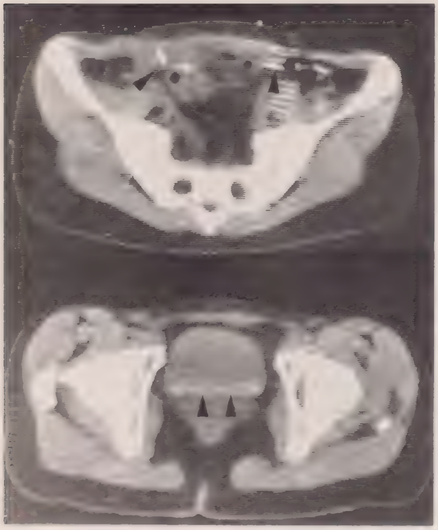
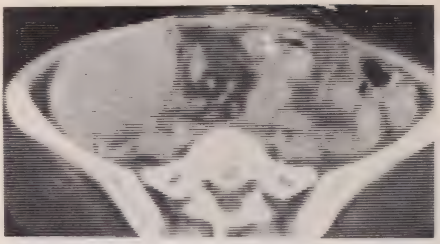


Fig. 5. Recurrent Crohn's disease. CT scan after sinogram: 2 enterocutaneous fistulas (arrowheads, above) and small amount of contrast medium in bladder (arrowheads, below) from enterovesical fistula (diagnosis proved at surgery).



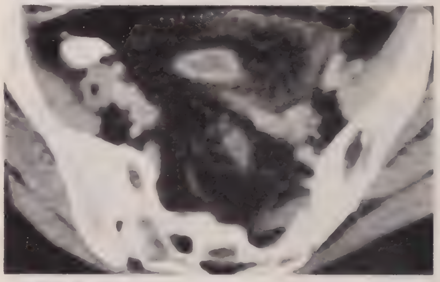


Fig. 6. Top Poorly differentiated adenocarcinoma arising in small-bowel segment affected by Crohn's disease. CT scan: large right lower quadrant mass lesion (at laparotomy, resection margins were free of tumor but contained active Crohn's disease).

Fig. 7. Bottom Nonstenotic regional enteritis of ileum, with extensive ulceration and irregular reticulated pattern on small-bowel study. CT scan: ulcerations of transmural disease.

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Intubation Infusion Method: Reliability in Diagnosis of Mechanical Partial Small-Bowel Obstruction

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Abstract

Fifty-six patients with suspected partial small-bowel obstruction were evaluated by the intubation infusion method, or enteroclysis, in a five-year period. Mechanical partial obstruction was diagnosed by this method in 38 patients. Of the 24 patients who went to surgery, the diagnosis by enteroclysis was confirmed in 23. In the single false-positive enteroclysis, the obstruction had been interpreted as "minimal." Thirteen remaining patients with positive enteroclysis had conservative management. Enteroclysis excluded the possibility of significant mechanical obstruction in 19 patients. There were no complications associated with the procedure. Enteroclysis is an accurate and rapid method in the evaluation of partial small-bowel obstruction.

The radiologic examination is the most important of all special methods of inquiry in the diagnosis of intestinal obstruction (1). The accurate pre-operative diagnosis of a complete or almost complete mechanical small-bowel obstruction is high when the clinical findings of crampy abdominal pain, vomiting, distention, and obstipation are correlated with the radiologic findings of small-bowel distention, multiple air fluid levels, and decreased colon gas and fecal material. Unfortunately, the pre-operative evaluation of partial or intermittent small-bowel obstruction is considerably more difficult. Delay in diagnosis and inappropriate management is common. Too frequently, complete obstruction supervenes and the correct diagnosis is made only at laparotomy. The importance of early diagnosis in small-bowel obstruction demands and deserves a rapid and accurate diagnostic method. We report our experience with the use of intubation infusion techniques, or enteroclysis, in the evaluation of partial or intermittent small bowel obstruction. Unfortunately, this useful and practical method has not been emphasized in the literature.

Methods

Patients clinically suspected of having partial small-bowel obstruction who were admitted to the Methodist Hospital of Indiana in a five-year period (January 1977 to January 1982) and who were examined by enteroclysis are included. Patients who were admitted for other diagnoses but who developed symptoms of small-bowel obstruction and had enteroclysis were also included. Nine of the 56 patients had conventional small-bowel follow-through examinations.

Details of the enteroclysis method have been described previously (2, 3). Briefly, a barium suspension of preselected concentration was infused through a tube introduced transnasally or perorally into the distal duodenum or proximal jejunum (4). The site of obstruction was identified by stasis of the head of the barium column and a change in caliber between the distended loop proximal to and the collapsed or normal caliber segments distal to the obstructing lesion (Fig. 1). The passage of barium through the area of narrowing was followed to the cecum to detect multifocal involvement or associated abnormalities (Fig. 1). Radiographs were obtained in the prone position with tube angulation or in the supine

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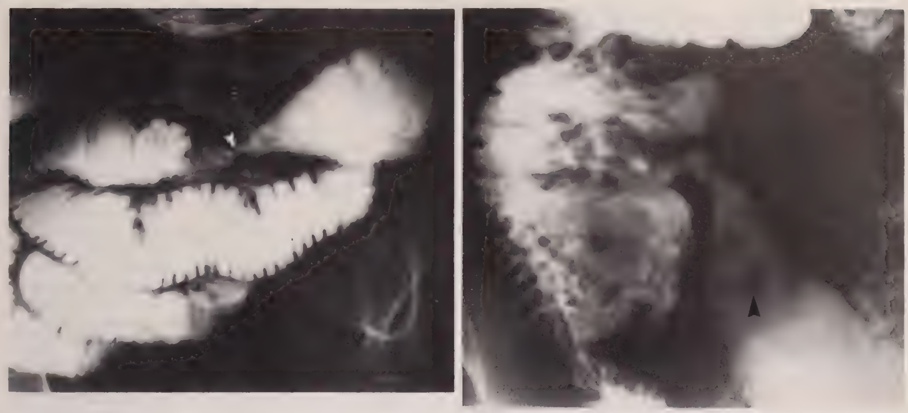

Fig. 1. **Left** Partial obstruction, proximal jejunum secondary to stenosing Crohn's disease. Note moderate dilatation proximal to stricture and normal caliber distal to obstruction. A tight obstruction results in collapsed segment distal to point of obstruction. **Right** Involvement of distal ileum clearly demonstrated in spite of proximal obstruction; aphthous ulcer (arrowhead).

position with compression and tube angulation. The examination is usually completed in approximately 15 to 30 minutes.

Results

During the five-year period, 56 patients with suspected small-bowel obstruction were examined by enteroclysis and each had more than six months' follow-up. Nineteen of the enteroclysis examinations showed no obstruction. This allowed appropriate restructuring of the clinical work-up. Five of these "no obstruction" patients eventually went to surgery, and the surgical findings confirmed the enteroclysis interpretation. In three of these patients, abnormalities which could potentially cause obstruction were successfully detected. One patient had a small reducible inguinal hernia; another had a fixed, kinked segment of ileum; and another had a small, intramural, extramucosal defect which proved to be a malignant carcinoid tumor (Fig. 2). The two other patients who had normal enteroclysis and who went on to autopsy or surgery were confirmed as having a normal small bowel.

Thirty-seven enteroclyses were interpreted as positive for small bowel obstruction. In the 24 patients that immediately went to surgery, the enteroclysis result was confirmed in 23 (Table). The one "false positive" enteroclysis was radiologically interpreted as showing evidence of minimal obstruction. A uterine fibroid was found at surgery, but no evidence of small-bowel adhesions was seen. Among the twenty-three patients whose enteroclyses were positive, there were six obstructing lesions located in the jejunum, four in the mid-ileum, and thirteen in the distal ileum (Fig. 3). Thirteen patients with a positive enteroclysis had conservative therapy (Fig. 4, Table). Two of these patients eventually had surgery and the diagnoses were confirmed. One had carcinomatosis and the other had an ileocecal adhesion adjacent to an intramural appendiceal mass shown at surgery to be an appendiceal mucinous cystadenoma. Nine of the 37 patients who had positive enteroclyses had conventional small bowel follow-through examinations. In 6 patients who went to surgery following these examinations, there were 3 false-negative and 2 false-positive examinations. In only one case was the impression from the small-bowel follow-through examination confirmed.

Discussion

Small-intestinal obstruction, when tight, can be diagnosed in the majority of patients on the basis of the clinical findings and plain abdominal radiographs (5, 6), and no further investigation is needed. However, the clinical suspicion of mechanical partial small-bowel obstruction may not be corroborated by the plain radiographs. The plain radiograph may be normal or there may be a paucity of gas in the distended small-bowel loops because of excess fluid (7).

The numerous reported radiographic techniques of small-bowel examination reflect the difficulty encountered in the early diagnosis of small-bowel lesions (8–10). In our experience, the direct infusion of barium through a tube positioned in the distal duodenum or proximal jejunum has proved most informative in the evaluation of partial small-bowel obstruction. The level of obstruction as well as the nature of the obstructing lesion has been demonstrated in most cases. In our study, one false positive and no false negative enteroclyses were seen. In these same patients, there were three false negative and two false positive conventional follow-through examinations. The limitations of the follow-through examination in the evaluation of minimal obstructive lesions (11) have been shown. The inability to challenge the elasticity of the bowel wall, the unreliable timing of the usual serial examination, and a prolonged procedure are significantly limiting factors in the conventional method. There is often retention of contrast medium in the stomach with delayed and incomplete filling of the small bowel. Because of slow and intermittent filling of the small bowel, contrast proximal to the site of obstruction is increasingly diluted and mucosal detail is inadequate. Serial examination up to twenty-four hours is not infrequent and this further limits anatomic detail. Partially obstructing lesions may only produce a fleeting moment of prestenotic dilatation resulting in a false negative conventional small-bowel examination in the evaluation of mechanical obstruction.

The ability of the infusion method to challenge the elasticity of the bowel wall accounts for the striking prestenotic dilatation even in instances of minimal obstruction. In addition, the presence

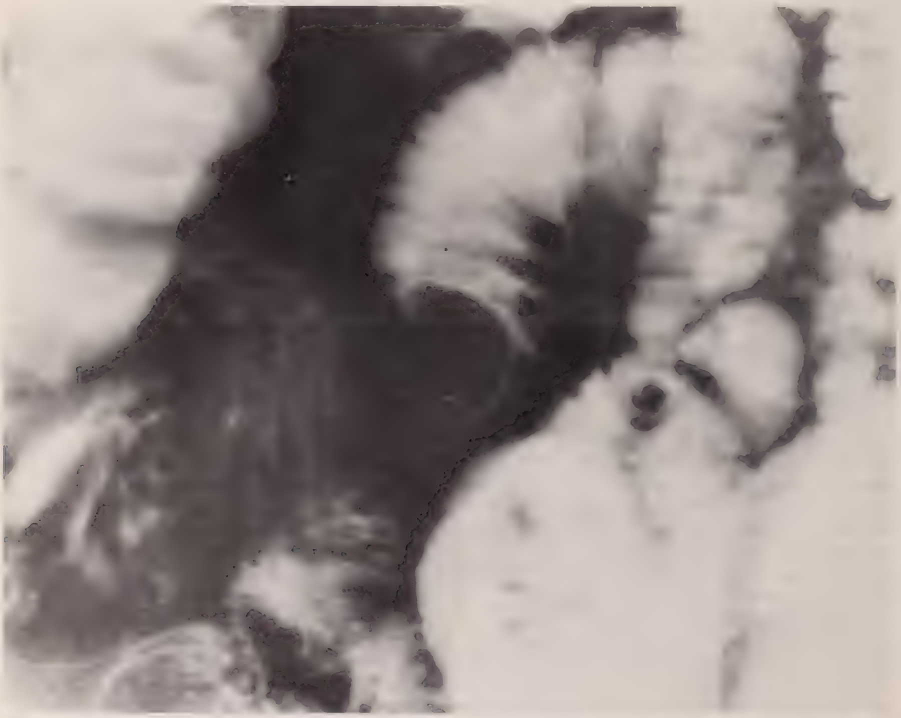

Fig. 2. Small intramural extramucosal mass in patient with intermittent abdominal pain and distention of one year's duration. The small-bowel follow-through was reported as normal. Surgery revealed a malignant carcinoid.

TABLE
Positive Enteroclysis for Obstruction

Final Diagnosis	No. of Patients
With surgical confirmation	
Adhesive bands from prior surgery	10
Small-bowel fistula, associated adhesions	2
Chocolate cyst, associated adhesions	1
Infarcted epiploic appendage, associated adhesions	1
Crohn's disease, ileum and jejunum	3
Metastatic carcinoma	2
Radiation enteritis	1
Meckel diverticulum, perforated	1
Ileocolic intussusception	1
Ileocecal valve carcinoma extending to distal ileum	1
Managed medically	
Adhesive bands	7
Metastatic disease	2
Crohn's disease	3
Ischemic enteritis	1

of the fluoroscopist at all stages of small-bowel filling increases sensitivity for subtle findings. Compression of a moderately distended segment also makes evaluation of small intramural defects easier. It is common to see fused pelvic segments of ileum secondary to adhesions. In these instances, the conventional small-bowel follow-through will result in clumped featureless pelvic segments of ileum, and a diagnosis is difficult and many times not possible. This problem can often be overcome during enteroclysis with the use of methylcellulose or air to produce a double contrast, see-through effect.

When searching for the site of obstruction, attention must be directed toward identifying the level of caliber change, either from a distended segment proximal to the obstruction or a collapsed or normal lumen distal to the obstruction. The infusion method makes identification of obstruction simple. The high reliability of a positive or negative enteroclysis examination, as shown in this series and by others, emphasizes the importance of the infusion method in the evaluation of partial or severe obstruction (12). This is invaluable information because, of the more common abdominal surgical emergencies, intestinal obstruction is wrongly diagnosed most often (13). Some patients with demonstrable obstruction will respond to conservative management, though many of them will subsequently require surgery (14, 15). Thirteen of our patients with an abnormality demonstrated by enteroclysis initially responded to conservative therapy. Knowledge of the level, degree, and probable cause of obstruction is valuable information in planning the appropriate course of management. The only contraindications to enteroclysis are suspected perforation or a high probability of complete obstruction in the colon. In the latter event, a barium enema with retrograde filling of the distal small bowel (retrograde small-bowel enema) should be the examination of choice (9, 10).

There has been reluctance to use barium for contrast examination of the obstructed small bowel for fear of converting a partial to a complete obstruction by barium impaction. It has been shown by animal and human studies that barium will not convert a partial small bowel obstruction into a complete obstruction by impac-

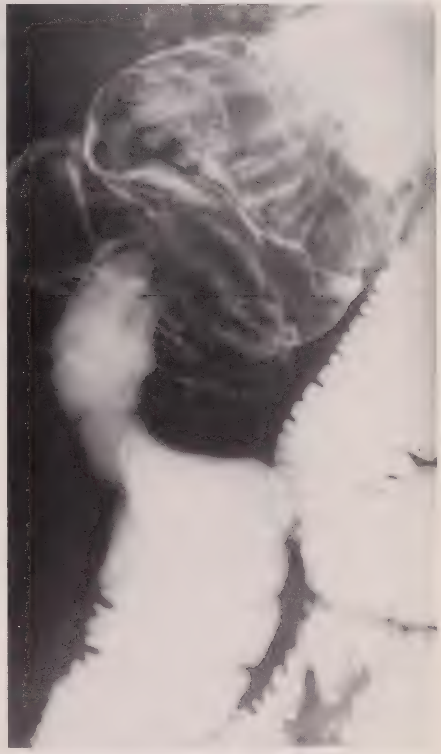

Fig. 3. Ileocolic intussusception in patient with symptoms of intermittent obstruction of six months' duration following appendectomy. Small-bowel follow-through examination done during an asymptomatic interval was normal. Lead point of intussusceptum was granuloma of appendiceal stump.

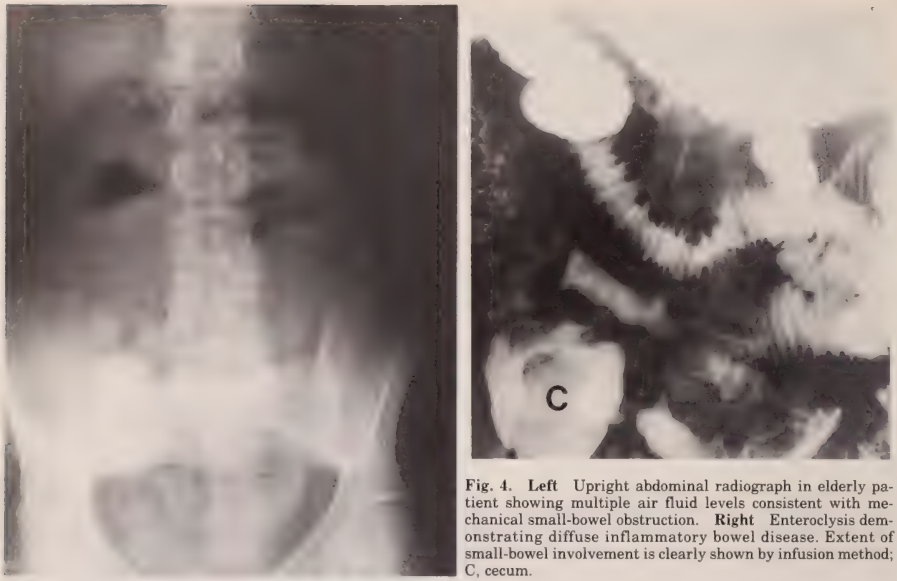

Fig. 4. **Left** Upright abdominal radiograph in elderly patient showing multiple air fluid levels consistent with mechanical small-bowel obstruction. **Right** Enteroclysis demonstrating diffuse inflammatory bowel disease. Extent of small-bowel involvement is clearly shown by infusion method; C, cecum.

tion (16, 17). The presence of barium in the bowel in the few patients who require early surgery is not an obstacle to laparotomy. Water-soluble contrast medium is inferior to barium in the diagnosis of intestinal obstruction. Because of its high osmolarity, it attracts additional fluid into the lumen and is diluted to a poor contrast agent; in addition, this medium can cause dehydration and electrolyte imbalance (18). Water-soluble contrast, however, remains the agent of choice in patients where perforation is suspected. However, these are usually diagnosed by demonstrating a pneumoperitoneum (19).

The usefulness of the conventional small-bowel examination, using survey films and fluoroscopy, in high grade obstruction has been shown (8, 17). Unfortunately, this technique takes time and has significant limitations in the evaluation of a partially obstructing lesion (11, 19). Distensibility and fixation of the small bowel are not tested. A negative examination is unreliable (11). The small size of the enteroclysis tubes (12–14 F) and the speed with which they can be positioned at the duodenojejunal segments (approximately 1–3 min) have partially negated the inherent disadvantages of the enteroclysis technique (3). The speed with which the examination can be performed and its ability to challenge the elasticity of the bowel wall and to exaggerate the effects of minimal obstruction make enteroclysis a more appropriate examination for partial small-intestinal obstruction (20). The method is capable of precise demonstration of the level of obstruction and also of the nature of the obstructing lesion.

Summary

Intubation infusion examination is a valuable method in the confirmation or exclusion of partially obstructive small-bowel lesions. The mucosal detail of the small bowel is rapidly and accurately evaluated during antegrade infusion of barium through a small tube positioned in the duodenojejunal junction. The reliability of a positive or negative examination is high (21). The practical usefulness of this method for both the attending physician and patient and its speed and precision should be more widely understood, and the method should be more widely adopted.

Acknowledgment

We thank Fran Shaul for secretarial assistance.

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Diagnosis of Meckel's Diverticulum in Adults

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Abstract

It is generally agreed that technetium 99m pertechnetate scanning is a highly sensitive test for the diagnosis of Meckel's diverticulum in children. It came to our attention that a series of technetium scans carried out on adult patients had failed to reveal a single case of Meckel's diverticulum. This observation prompted us to embark on a study to determine which currently available method is the most efficient for the detection of this condition in adults. To this end, we reviewed the records of all patients on whom a laparotomy had been performed in the Toronto General Hospital between 1970 and 1981 and identified 40 cases of Meckel's diverticulum proven at surgery. Nine patients had conventional small-bowel studies, but only one was correctly diagnosed as having a Meckel's diverticulum (11%). Six patients had technetium 99m pertechnetate scans and none were positive. Enteroclysis (small-bowel enema) was performed in 8 patients, and Meckel's diverticulum was found in 5 (63%). We conclude that in adults, enteroclysis is more sensitive than technetium 99m scanning in the diagnosis of Meckel's diverticulum. The reasons for the reduced effectiveness of radionuclide scanning are discussed.

Meckel's diverticulum causes symptoms quite often in pediatric patients but only occasionally in adults. When the condition is suspected in an adult, a technetium 99m pertechnetate scan has been considered the investigation of choice, on the presumption that the high diagnostic yield of 75%–90% which occurs in children (1) can be achieved for adults. However, our own experience with radionuclide scanning in adults has not been rewarding.

Since enteroclysis (small-bowel enema by intubation) had been reported useful for the detection of Meckel's diverticulum (2, 3), we felt the need to assess the relative effectiveness of technetium 99m scan, enteroclysis, and the conventional small-bowel series in the diagnosis of suspected Meckel's diverticulum in adults.

Methods. Our review of the medical records of all patients who had laparotomy at the Toronto General Hospital between 1970 and 1981 identified 40 cases of surgically proven Meckel's diverticulum. This study is based on analysis of these 40 cases by clinical presentation, diagnostic workup, and pathological finding (in particular, the presence or absence of ectopic gastric mucosa in the Meckel's diverticulum).

The techniques of enteroclysis have been described in detail (4). Briefly, duodenal intubation with a Bilbao-dotter tube was achieved, and the catheter tip placed to the ligament of Treitz. One liter of 45% w/v barium-sulphate suspension (Barosperse) was delivered by gravity to the small intestine from four feet above the table top. If the cecum was not reached after the infusion, 600 ml of water was added to advance the barium column. Intermittent fluoroscopy of small-bowel loops and spot films were undertaken.

When a small-bowel series was performed, a total of 500 ml of 80% w/v barium-sulphate suspension was ingested by the patient, and sequential abdominal films were taken. When the barium column reached the terminal ileum or when an abnormality was detected on fluoroscopic examination, a film of the terminal ileum or the abnormality was obtained.

For radionuclide scanning, a dose of 10 mCi of technetium 99m pertechnetate was given by intravenous bolus injection. A dynamic study was performed immediately. The vascular phase was recorded at 2–3 secs per frame for the first seconds, with the patient in the anterior supine po-

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sition. Following this, serial 500K-count anterior images were obtained at intervals of 5 min for a further 25 min. At 30, 45, and 60 min, a set of anterior, right lateral, and posterior views were obtained. If an area of abnormal increase in uptake was observed, further views including obliques, upright, and posterior images were obtained.

Results. The diagnosis of Meckel's diverticulum was confirmed, at surgery, in 40 adult patients—20 women and 20 men, mean age 45 years (range 20–80 years).

Twenty-four patients (60%) had no symptoms related to the Meckel's diverticulum, which was found incidentally at surgery for other diseases, most commonly Crohn's disease. Of the 16 patients (40%) in whom symptoms could be attributed directly to the Meckel's diverticulum, 5 (31%) had gastrointestinal bleeding, while the other 11 (69%) had symptoms related to peritoneal inflammatory process or small-intestine obstruction. Ectopic gastric mucosa was found in 8 patients.

Six patients had technetium 99m pertechnetate scans. Notwithstanding the presence of ectopic gastric mucosa in the Meckel's diverticulum of 2 patients, there were no positive scans. Neither of the 2 patients, who had scans for gastrointestinal bleeding, had ectopic mucosa in their Meckel's diverticulum.

Although a conventional small-bowel series had been performed in 9 patients, only 1 (11%) was found to have a Meckel's diverticulum.

Enteroclysis had been performed in 8 patients. The indication for this examination included intestinal obstruction (3 patients), gastrointestinal bleeding (2 patients), and Crohn's disease (3 patients). A radiologic diagnosis of Meckel's diverticulum was correctly given for 5 patients (63%). Two of the patients, in whom gastrointestinal bleeding was the presenting feature, had a radionuclide scan, small-bowel series, and enteroclysis. Only the enteroclysis showed the Meckel's diverticulum in these 2 patients. Subsequently, it was discovered that in these 2 patients the Meckel's diverticulum was not lined by ectopic gastric mucosa.

Discussion. Several publications have referred to the difficulty and indeed the futility of the conventional small-bowel series in searching for a Meckel's diverticulum, both in the pediatric and adult populations (5–8). For adults, our results (11%) would support these reports. The small size of the diverticulum, rapid emptying of barium, wide ostium, or a stenosis have all been cited as possible explanations for the poor results achieved with this radiologic procedure (3).

Although approximately 10%–16% of all Meckel's diverticula are lined with gastric mucosa (9, 10), the incidence is variably reported to increase in symptomatic patients to 30%–65% (10–11). In infants and children with gastrointestinal bleeding, the incidence is reported to be near 100%, as illustrated by one large series (12), in which 42 of 43 patients were shown to have gastric mucosa in the Meckel's diverticulum.

Since radionuclide scanning for Meckel's diverticulum depends on the uptake and concentration of technetium 99m pertechnetate by the ectopic gastric mucosal lining, the diverticulum scanning is frequently considered and cited to be the procedure of choice in establishing the diagnosis in children. Our finding has provided empirical evidence that the extrapolation of this conclusion to adults is invalid. The reason for this is that the prerequisite for the success of radionuclide scanning, namely, presence of ectopic gastric mucosa, is present much less frequently in adults than in children.

In two larger series (9, 10) of a mixed pediatric and adult population with gastrointestinal bleeding, the incidence of ectopic gastric mucosa was 60% to 68% (9, 13), somewhat lower than the near 100% cited above. Moreover, even when ectopic gastric mucosa is present, the false negative rate with scanning may be as high as 50% (10, 14), while there is also a false positive rate of 9%

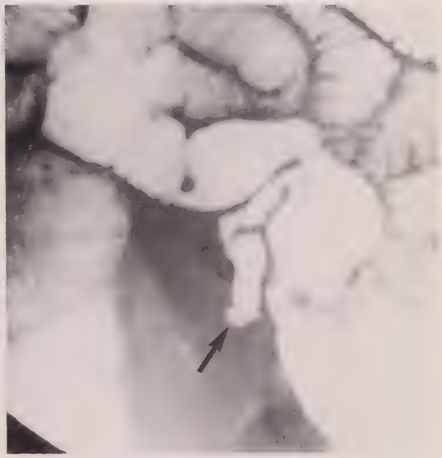

Fig. 1. Enteroclysis showing small Meckel's diverticulum on antimesenteric border.

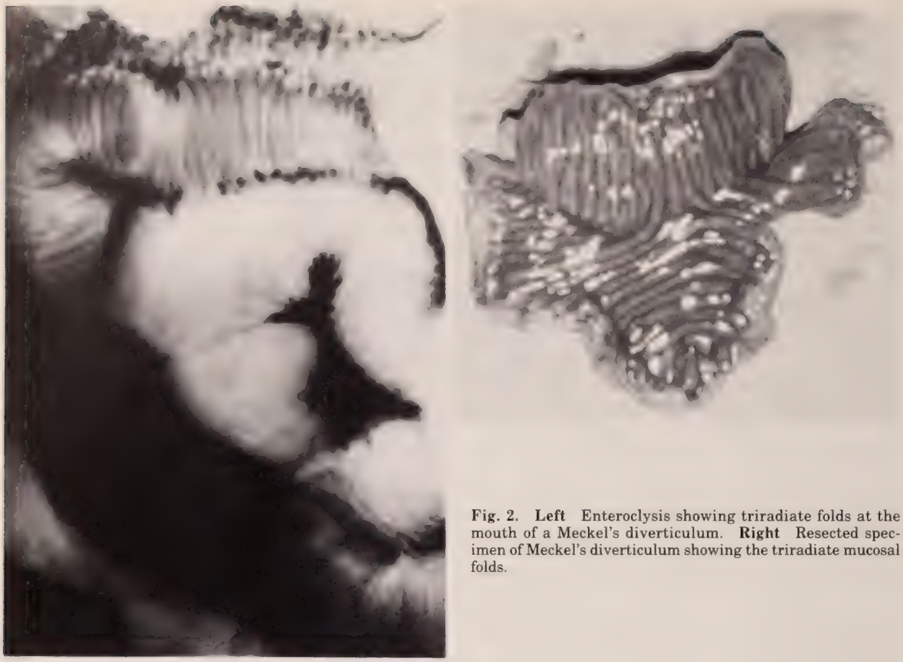

Fig. 2. Left Enteroclysis showing triradiate folds at the mouth of a Meckel's diverticulum. **Right** Resected specimen of Meckel's diverticulum showing the triradiate mucosal folds.

(15). In our 5 patients with gastrointestinal bleeding, 3 had ectopic mucosa, which accords well with the experience of others. None of this group of 3 had technetium scans. In 2 of our patients, bleeding had occurred from ulcers within the Meckel's diverticulum that contained no ectopic gastric mucosa.

An alternative procedure with a better yield, regardless of the presence or absence of gastric mucosa, is required for the diagnosis of Meckel's diverticulum in adults. The advantages of enteroclysis were discussed as early as 1954 (16). Sellink (2) and Maglinte (3) have both reaffirmed its value in detecting Meckel's diverticulum. Our results confirm and extend their observations by demonstrating that enteroclysis has a substantially higher yield over radionuclide scanning or the conventional small-bowel series in the diagnosis of this condition in adults. Several factors may have contributed to this result, including full distention and complete filling of the small bowel, as well as intermittent fluoroscopy.

Radiologically, the Meckel's diverticulum is easy to identify if it shows a blind pouch in the distal ileum (Fig. 1). On fluoroscopy, it contracts like the rest of the small bowel. It differs from acquired diverticula by its antimesenteric location, and it can be identified by triradiate folds at the mouth of the diverticulum (Fig. 2). Differentiation from pseudosacculation, as found in Crohn's disease, is made by the absence of other radiologic stigmata of the disease in adjacent and other segments of the small intestine.

Conclusion. Although radionuclide scanning is an extremely useful tool in the diagnosis of Meckel's diverticulum for patients in the pediatric age group, it is much less valuable in the adult population. This is mainly due to the lower incidence of ectopic gastric mucosa in adults. Our study shows enteroclysis is more sensitive in the diagnosis of this rare entity in the adult population.

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Small-Bowel Changes Secondary to Intraperitoneal Leakage from Dermoid Cyst of the Ovary

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Abstract

Granulomatous chemical peritonitis secondary to acute rupture of, or slow leakage or surgical spillage from, a dermoid cyst of the ovary has been found at surgery or autopsy in approximately 100 reported patients. When this is chronic, the clinical presentation is suggestive of primary gastrointestinal disease and is nonspecific. At surgery, the gross appearance is similar to that of tuberculous peritonitis or carcinomatosis. The patient reported here illustrates the changes provoked by this irritating material as documented on preoperative barium studies. The association of a pelvic mass and an abnormal small-bowel study in a woman with moderate gastrointestinal complaints, including diarrhea, should alert one to this possible diagnosis.

Rupture of an ovarian dermoid cyst (benign cystic teratoma) is a rare complication of a relatively common benign tumor. When this rupture is acute and extensive, surgery is clearly required, and barium studies will usually not be requested. At times, however, slow leakage of this irritating material occurs, and the clinical presentation becomes one of nonspecific gastrointestinal disease. Such a case was studied and, during the course of the diagnostic work-up, a grossly abnormal small-bowel pattern was demonstrated. Although these abnormalities have been seen often at surgery, this case is believed to be the first roentgenographic demonstration of the small-bowel changes secondary to the granulomatous chemical peritonitis provoked by leakage of this irritative material from an ovarian dermoid cyst.

Case Report

A 35-year-old, single, nulliparous white woman was admitted to Mount Zion Hospital and Medical Center with a four-month history of diarrhea, increasing abdominal distention, and ten-pound weight gain. Abdominal pain, mostly on the right side and occasionally crampy in nature, had been present for several weeks. Some anorexia was present, although she said that she had not been subject to nausea or vomiting. Formerly, her bowel habits had consisted of one normal bowel movement every three to four days, but during this period she was experiencing a daily semiliquid stool with intermittent episodes of severe diarrheal movements. She had observed no melena or gross blood in the stools, and she had no past history of gastrointestinal disease. In the few weeks prior to admission, the patient ran a constant low-grade fever for which she had received tetracyclines without relief. An oral cholecystogram obtained prior to admission was normal.

Physical examination revealed the patient to be slightly obese and in mild distress, with normal vital signs and a temperature of 99°F. The abdomen was moderately protuberant with right upper quadrant and midepigastric tenderness with some rebound. Moderate guarding was present and bowel sounds were active. No masses were felt. The rectopelvic examination was difficult to perform but was considered to be negative.

Pertinent laboratory data included a hemo-

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globin value of 11.4 gm/100 ml and a white blood cell count of 10,500/mm^3 with 74% neutrophils. Serum amylase and lipase were normal. The stool was negative for occult blood, and sigmoidoscopy was negative to 12 cm. A barium enema on the second hospital day revealed a homogenous pelvic mass, with a normal large bowel and an abnormal distal small-bowel pattern. Because of the latter, a small-bowel series was obtained on the same day (Fig. 1). Although this was somewhat atypical of terminal ileitis, such was the roentgenographic diagnosis, along with an unrelated uterine or ovarian mass. An intravenous urogram confirmed the pelvic mass but was otherwise normal.

The patient was treated with sulfasalazine (Azulfidine), but this aggravated the gastrointestinal symptoms. A short course of steroids was administered prior to laparotomy, which occurred on the eleventh hospital day. At laparotomy, the peritoneum was markedly thickened, and there were 600 cc of fluid associated with "tenacious thickened yellowish-whitish material" adherent to the bowel and omentum. The small bowel was edematous and erythematous, especially the terminal ileum, and the entire bowel was studded with the tenacious material. Several loops of distal small bowel were fixed and their walls semirigid. Adhesions along the superior aspect of the liver under the diaphragm were present. A 5 cm right ovarian cyst was found deep in the cul-de-sac. The entire cul-de-sac was covered with the same thickened exudate, as were the posterior and lateral surfaces of the uterus and left ovary. The cyst was noted to be leaking a sebaceous material, and hair was present both inside the cyst and in the peritoneal cavity. The peritoneal cavity was lavaged with saline solution, and the adhesions were lysed.

The 100-gram cyst contained creamy, whitish material and was a typical dermoid cyst. Microscopic examination of the substance covering the peritoneum and bowel wall revealed necrotic material with numerous polymorphonuclear cells and a few histiocytes. Some fragments of keratin material were present. This material was similar to that in the cyst. Peritoneal fluid showed no growth at 72 hours, and all smears were negative. Culture for tuberculosis revealed no growth at two months.

The postoperative course was uneventful except for a mild paralytic ileus and a low-grade fever for two days. The patient has had no recurrence of symptoms, and a repeat small-bowel series 26 days post surgery (Fig. 2) revealed a normal small-bowel pattern.

Discussion

Benign cystic teratoma is one of the most common of ovarian neoplams, comprising up to

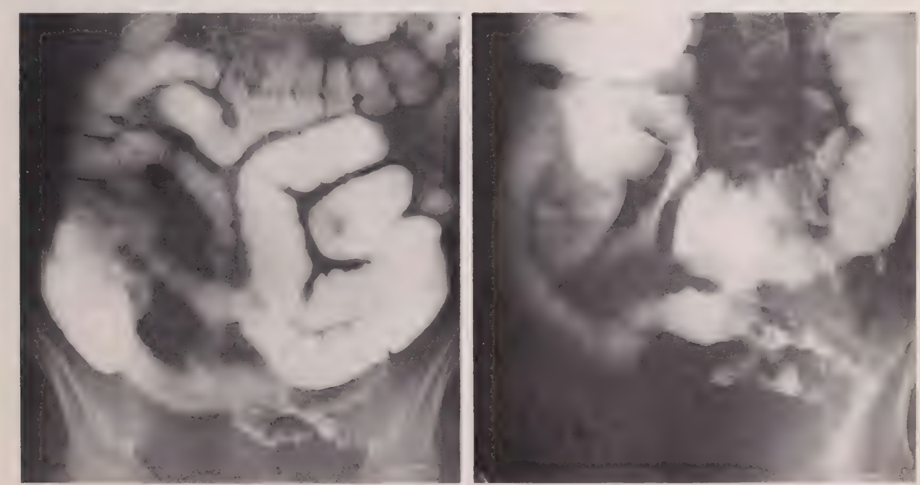

Fig. 1. Left Three-hour film in small-bowel series. Loops of distal small bowel are separated, have rigid and irregular walls with evidence of intramural edema. Pelvic mass is present. Much of barium in colon remains from immediately preceding barium enema. **Right** Oblique view film at 3$^1/_2$ hours.

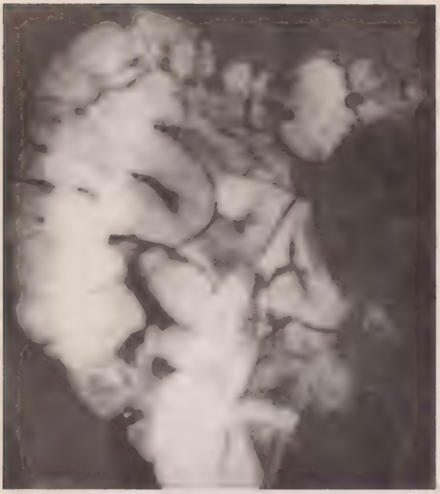

Fig. 2. Normal small-bowel series 26 days after laparotomy and cyst removal.

15% of all ovarian tumors (1, 2). The majority are discovered in the 20 to 40 age group. Pain is the most common complaint, and was present in about half of the 1,007 cases presented by Peterson et al (3). An abdominal mass or swelling was present in 15%. Other symptoms are noted less frequently, and 25% to 40% of such cases are asymptomatic. The correct preoperative plain film diagnosis is dependent on the presence of calcifications, including teeth, and on a relative lucency caused by the high fat content usually present (4). Ultrasonography may be helpful, 33% of the 51 tumors reported by Laing et al (5) having the "typical" appearance of an echogenic focus with acoustic shadowing situated within a predominantly cystic mass. Unfortunately, 23.5% were predominantly solid, 20% almost entirely cystic, and 23.5% were not visible. Twenty-three of their patients had plain films, 48% suggestive of the correct diagnosis, 39% indicating a nonspecific mass, and 13% negative.

The complications of benign cystic teratomas are those common to all ovarian cysts, namely torsion, infection, rupture, dystocia of pregnancy, and malignant degeneration. Of these, only torsion has been reported with any frequency, with an incidence of about 16% (3). Rupture occurred in 1.2% of reported cases. This includes rupture into a hollow viscus, such as the urinary bladder, intestine, rectum, or vagina, an entirely different entity than what we are presenting. Adhesions between the cyst and one of these structures, which may result from infection or torsion of the pedicle, must occur prior to rupture into such viscera (6). Rupture through the anterior wall of the rectum may occur acutely during forceful labor. Approximately 1% of all reported cases have shown malignant degeneration.

Dermoid cysts are reported to rupture less frequently than other ovarian tumors, apparently because of the thickness of the cyst wall. Stern et al reported only four ruptures in a series of 569 cases (0.7%), two of these intraperitoneal and the other two the less common rupture into a viscus (2). The clinical findings are dependent upon the acuteness of the rupture. In the acute type, an abdominal crisis may develop, and, prior to 1924, fatalities were not uncommon (7). If the patient survives the acute phase without surgery, or if there is slow leakage, as in our case, the symptoms may be relatively mild (8). With chronic leakage, progressive abdominal distention, associated with mild gastrointestinal disturbance such as anorexia, nausea, vomiting, and diarrhea, is the usual presentation.

Intraperitoneal rupture has been reported following external trauma (9, 10), the trauma of labor (11–16), including the use of forceps (7), needle aspiration (18), open biopsy (19), and accidental rupture during surgical excision (20). A large number may be secondary to torsion (21) while a few are infected (22). For many there is no apparent etiology, and Abitbol et al (8) found this to be true in 18 of 43 reviewed cases. Our case, likewise, appears to have been spontaneous.

The peritonitis produced by spillage of the contents of the dermoid cyst has been described as "chemical." The reaction by the serous surfaces results in a chronic granulomatous appearance with small yellow-white nodules. This appearance grossly is difficult to distinguish from tuberculous peritonitis and carcinomatosis (13). The granulomata microscopically are composed of lipoid-laden macrophages, lymphocytes, plasma cells, and foreign-body giant cells (7). This is the typical response of the body to a variety of intraperitoneal irritants, including the operative instillation of mineral oil and response to corn and rice starch powder from surgical gloves (23). Keratin and sebum are among the most potent granuloma producers, with keratin granulomata not uncommon in skin and oral mucosa (17). Unlike the self-limiting peritonitis associated with the cornstarch powder, the process associated with leakage from a dermoid cyst will continue until operative intervention with removal of the cyst.

The roentgenographic appearance is similar to

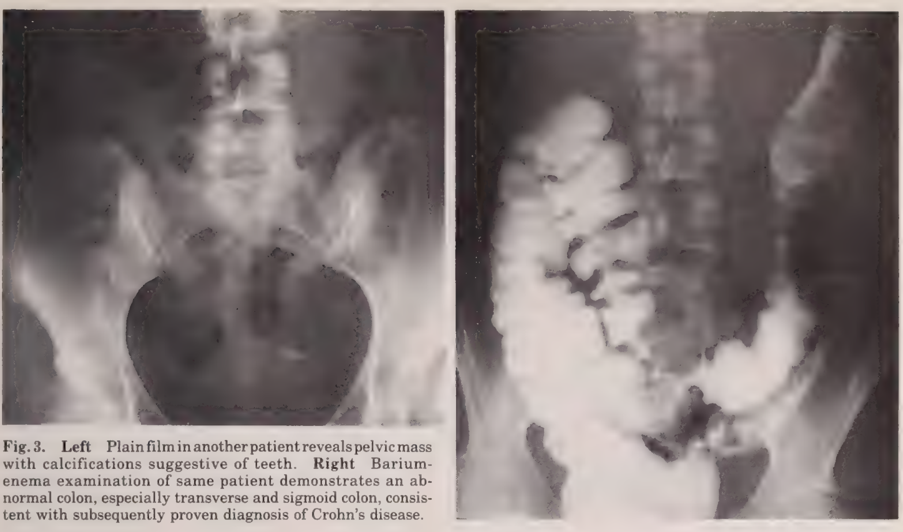

Fig. 3. Left Plain film in another patient reveals pelvic mass with calcifications suggestive of teeth. **Right** Barium-enema examination of same patient demonstrates an abnormal colon, especially transverse and sigmoid colon, consistent with subsequently proven diagnosis of Crohn's disease.

that seen in the enteritis of Crohn's disease, radiation, tuberculosis, and ischemia, as well as in intramural hemorrhage from various causes. Somewhat similar changes have been reported in gold salt injection (24) and in granulomatous peritonitis due to coccidioides immitis (25). Although the etiology in each of these may well be quite different from the others, the bowel has only a limited variety of responses to irritants. The rapid return to a normal appearance postoperatively in our patient confirms the exudative, intramural nature of the radiographic changes.

We have reviewed the nearly 100 reported cases and have found no illustrated examples showing an abnormal small-bowel pattern discovered in a preoperative study. A case report by Waxman and Boyce (26) without an illustration described an upper gastrointestinal examination to show "irregularity of small bowel loops, consistent with a peritoneal inflammation." A few barium-enema studies have demonstrated a pelvic mass, although most of the patients did not have any contrast examinations reported.

It seems reasonable to expect additional cases to be encountered in the future with the increasing use of ultrasonography and computerized tomography in the evaluation of these diagnostic problems. Certainly, there is nothing specific about the barium studies to link these abnormalities with a discovered pelvic mass, which most often will still be an unrelated finding (Fig. 3). An awareness of this possible association, however, should help in the preoperative evaluation of difficult acute and chronic abdominal conditions. Intraperitoneal leakage from a dermoid cyst should be added to the long list of causes for an abnormal small-bowel pattern.

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Ultrasound and Computed Tomography in the Evaluation of Inflammatory Bowel Disease

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Ultrasound and computed tomography (CT) are commonly employed in the evaluation of intraabdominal and retroperitoneal pathology. Since becoming a routine and integral part of the radiologist's armamentarium, they have been shown to have many more applications than originally anticipated. One major area of use which initially received little attention in the literature was the gastrointestinal tract. Because of interference and artifacts created by bowel gas and mesenteric fat, ultrasonic evaluation of the intestine seemed to hold little promise. Likewise, images obtained on early CT scanners, which had long scan times, were significantly degraded by peristaltic motion. This made assessment of all but the most obvious abnormality of small or large bowel virtually impossible.

With the advent of real-time ultrasound and fourth-generation CT equipment having scanning times of less than five seconds, both methods have demonstrated definitive and unique capabilities in the evaluation of patients having gastrointestinal (GI) disease. In inflammatory bowel disease and related disorders, ultrasound and CT can complement standard barium studies and endoscopy. In the proper clinical setting, more conventional studies can even be bypassed in favor of these newer techniques.

Techniques

Ultrasound. Real-time (dynamic) ultrasound is to static scanning what fluoroscopy is to routine radiography. Segments of bowel can be identified by virtue of direct observation of peristalsis, and thus careful analysis of motility, degree of gaseous or fluid distention, and thickness of the bowel wall can be made.

In evaluating the stomach, duodenum, and proximal jejunum, having the patient drink water or some other appropriate "contrast agent," such as methylcellulose and water, can be helpful in deciding if a visualized structure represents a normal part of the GI tract. If a sufficient volume of fluid can be ingested at the time of scanning, the wall of the fluid-filled stomach or intestine can be demonstrated and measured.

Similarly, a water enema can be administered during dynamic scanning of the pelvis in order to verify the position and normality of the rectum and distal sigmoid colon. This is especially important when evaluating obscure pelvic masses which may mimic the normal nondistended or fecal-filled colon. In most examinations, the patient must have a full urinary bladder, which serves as an acoustic window through which the rectum and distal sigmoid colon can best be imaged. Superficial small bowel loops, the transverse colon, the cecum, and portions of the sigmoid colon, because of their proximity to the abdominal wall, can often be identified and assessed at the time of routine abdominal scanning.

Computed Tomography. Opacification of the stomach, duodenum, small bowel, and colon is essential for optimal CT examination of the abdomen and pelvis. Unopacified bowel can be misinterpreted as a pathologic process and vice versa. Nondistended bowel will appear to have thickened walls, due to the heaping up of mucosal folds. Liberal use of a dilute barium-sulfate suspension (E-Z Cat) or a one or two percent solution of iodinated contrast material (Gastrografin) administered orally or rectally is vital to success.

All of the small bowel can usually be opacified by oral administration of 600 cc of a contrast agent one hour prior to scanning, followed by an-

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other 300 cc 30 minutes later. To ensure adequate filling of the stomach, 300 cc of the contrast medium should also be ingested just before starting the examination. These techniques need to be modified if the patient is known to have a condition resulting in rapid gastric emptying or marked alteration of small-bowel transit time.

When attention is directed to the pelvis, 200 to 500 cc of a similar contrast mixture should be given as an enema immediately before scanning. This will generally fill the rectum, sigmoid colon, and distal descending colon. Segmental lack of distention can be avoided by intravenous glucagon. For visualizing the remainder of the colon with some consistency, it may be necessary to give the contrast medium by mouth several hours in advance of or on the evening before the scheduled examination. For women, a tampon in the vagina helps in identifying this structure.

Visualization and precise localization of fistulae and sinus tracts by CT is possible if contrast material is injected into a cutaneous opening just prior to scanning (1). Spontaneous opacification of such tracts is not reliable by routine methods; and they can be overlooked or their full extent may be underestimated.

Normal Bowel Anatomy

Ultrasound. The stomach, duodenum, small intestine, and colon all have a similar sonographic appearance when not distended by fluid. Since mucus is highly reflective of sound, the center of any segment of gut appears strongly echogenic compared to the more hypoechoic surrounding wall. Scans taken transverse to the longitudinal axis of bowel thus yield a characteristic "target," or "bull's-eye," pattern (2–4). The thickness of the normal bowel wall depends somewhat on the degree of distention but, in general, the sonolucent rim representing the wall should not exceed 5 mm or 6 mm (3), and it should be of uniform thickness, with symmetrical location of the central echogenic core (4).

Observation during dynamic scanning can easily confirm the identity of bowel by virtue of peristaltic activity. Not only is this important when fluid-filled loops of bowel mimic hypoechoic masses, such as enlarged lymph nodes, but the lack of normal peristalsis may signal the presence of an underlying pathologic process.

Computed Tomography. Determining the thickness of the normal bowel wall by CT is difficult since unopacified intestinal contents, mucosa, and the wall itself may all have similar attenuation values. If adequate distention with contrast material can be attained, scans taken transverse to or along the longitudinal axis of a segment of bowel afford very good visualization of the wall since it has a density intermediate between the surrounding mesenteric fat and the opacified lumen. The thickness of the large- or small-bowel wall should not exceed 4 mm by CT.

Abnormalities involving the bowel usually also have some effect on the surrounding mesentery. Normal mesenteric fat is of homogeneously low attenuation (−100 to −160 HU) except for small linear or punctuate densities representing blood vessels or lymph nodes. Mesenteric lymph nodes normally should not measure greater than 1 cm (5). Perirectal fat is fairly abundant, even in the very thin patient, and only fat density should be seen behind the rectum in the presacral space.

Crohn's Disease and Ulcerative Colitis

Inflammatory diseases of the bowel which result in morphologic changes in the mucosa lend themselves well to evaluation by endoscopy or conventional barium studies. Nevertheless, without some type of cross-sectional display, inflammatory changes involving layers of the wall deep to the mucosa, the serosa, surrounding mesentery or adjacent structures can only be inferred. CT and ultrasound thus play a complementary role in the diagnosis, evaluation, and followup of patients with Crohn's disease and ulcerative colitis.

It has long been recognized that the normal sonographic "target" configuration of the bowel is accentuated in patients with Crohn's disease because of submucosal edema, cellular infiltration, and fibrosis, which result in gross thickening of the sonolucent wall. Fluid and an influx of inflammatory cells in the adjacent mesentery probably contribute to this abnormally thick halo surrounding the hyperechoic mucosa. The appearance of such an involved segment of small or large bowel has been likened to that of the kidney, the thickened wall corresponding to the relatively hypoechoic renal parenchyma, and the mucosa resembling the central echo complex of the kidney (6). While this "pseudokidney" sign is somewhat nonspecific, its most common cause in the small bowel is Crohn's disease (Fig. 1).

Ultrasound examination of the abdomen is often the first diagnostic procedure requested for patients with abdominal pain or nonspecific intestinal complaints, making it possible to suggest the diagnosis of inflammatory bowel disease if the "pseudokidney" sign is recognized. Or, if this diagnosis has been made or is suspected on the

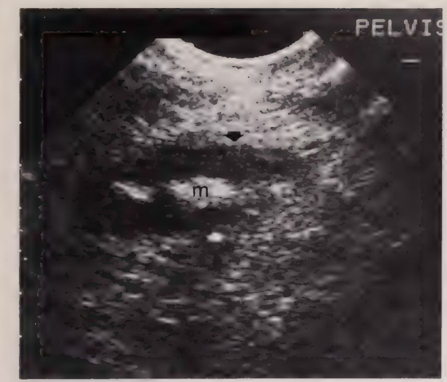


Fig. 1. Real-time demonstration of sonographic pseudokidney sign, a nonspecific indicator of diseased bowel. Abnormally thickened bowel wall (arrows) forms hypoechoic halo around echogenic mucosa (m). In this case of sigmoid diverticulitis, wall measures almost 1 cm thick. Appearance of involved small or large bowel in Crohn's disease is identical.

basis of other tests, ultrasound is useful in demonstrating extent of disease and in detecting abscess formation when contrast studies indicate separation of involved bowel loops (7). Since ileus or partial bowel obstruction may be present in these patients, care should be taken not to mistake fluid-filled bowel for an abscess. In addition to peristaltic motion seen with real-time ultrasound, demonstration of valvulae conniventes or haustral sacculations can help in making this differentiation (8).

Bowel-wall thickening is the most common CT finding in Crohn's disease (Fig. 2). In some instances this will result in the CT equivalent of the "string" sign, with a narrow, contrast-filled lumen passing through the center of a soft tissue mass representing the walls (9). Submucosal edema may be responsible for a middle layer of decreased attenuation lending a bull's-eye appearance to the ileum in cross-section (10). Presumably related to hyperemia incited by the inflammatory process, enhancement of the wall has been reported following administration of intravenous contrast material (11).

The major advantage of CT over both standard x-ray techniques and ultrasound is the ability to show changes within the mesentery adjacent to abnormal large- and small-bowel segments and within retroperitoneal compartments and the perirectal space. This is of paramount importance in evaluating inflammatory processes, especially Crohn's disease. Patients with this disorder frequently have signs and symptoms that suggest intraabdominal abscess or have a right lower quadrant mass evident by physical examination, barium enema, or a small-bowel series. Cross-sectional images provide an accurate assessment of the extent and severity of the extra-luminal inflammatory reaction.

Mesenteric fat may be normal in mild cases of Crohn's disease, with preservation of a sharply defined, smooth serosal surface bordering the involved bowel segments. With increasing severity of inflammation, the mesenteric fat undergoes an ill-defined, hazy increase in density, initially related to an influx of inflammatory cells and fluid (Fig. 2). This may then progress to more discrete nodular or streaky densities and then to large areas of confluent density, blending imperceptibly with the contiguous thickened bowel walls. Such extensive phlegmonous changes can explain the wide separation of small bowel loops seen on barium studies in these patients during acute exacerbations of their disease (Fig. 3). With time, the chronic inflammatory process results in proliferation of fibrous and fatty tissue, so-called "creeping" mesenteric fat (12).

While ultrasound is useful in screening patients for possible abscess, a false negative study may result from interference by air-filled loops of bowel or even air within the abscess itself. The diagnostic accuracy of CT in evaluation of intraabdominal abscesses has been shown to be

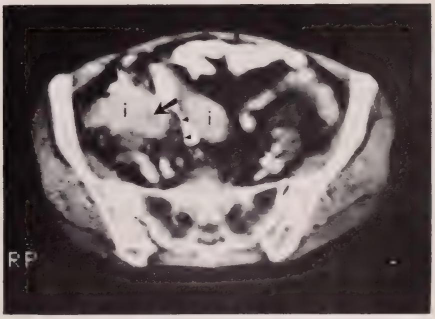


Fig. 2. CT of pelvis during acute exacerbation of known Crohn's disease. Thick-walled segments of terminal ileum (i) appear as soft tissue density masses in the right lower quadrant with essentially complete obliteration of bowel lumen. Barely detectable central area of lower density in one of these masses (arrow) probably represents unopacified fluid in narrowed lumen or submucosal edema. Adjacent mesenteric fat shows faint increase in density and contributes to extrinsic compression upon a nearby contrast-filled segment of small bowel (arrowheads).

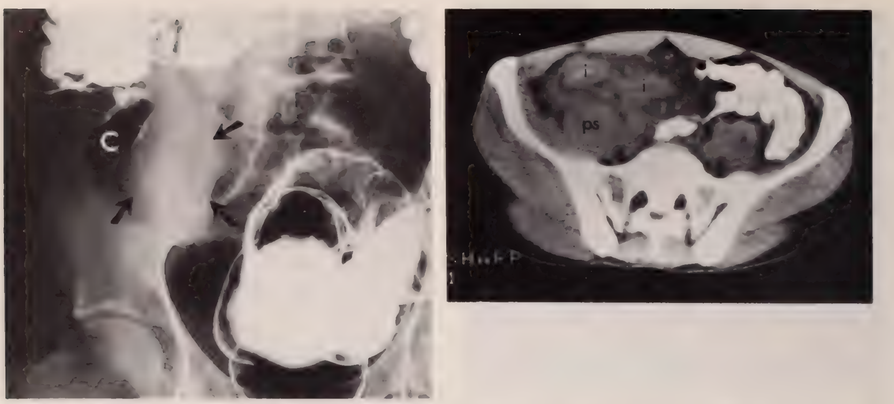


Fig. 3. **Left** Barium enema in a young man with right lower quadrant pain and a palpable mass. Distortion of cecum and ascending colon (C), dilated small bowel loops, and a soft tissue mass (arrows) suggest Crohn's disease; however, neither appendix nor terminal ileum could be filled. The possibility of abscess related to ruptured appendix or inflammatory bowel disease was entertained. **Right** CT two days after barium enema (ps = psoas muscle). Extensive inflammatory changes involving mesenteric fat result in large areas of increased density obscuring margins of thick-walled segments of distal ileum (i). Possibility of abscess could be excluded from CT findings; diagnosis of Crohn's disease was presumed, and patient improved following appropriate medical management.

96%, as compared to 90% for ultrasound (13). CT is not limited by the presence of intestinal or extraluminal gas, overlying dressings, or patient obesity. Demonstration of a fluid collection in the mesentery or retroperitoneum adjacent to affected bowel is strong evidence of an abscess, especially if bordered by a thick, enhancing wall. The presence of gas within the fluid, in the form of scattered bubbles or air-fluid levels, is virtually pathognomonic, but may be seen in only one-third to one-half of cases (13).

Differentiating phlegmon from abscess may be difficult by CT, because the attenuation values of phlegmon may approach those of fluid, and some abscesses containing very thick inflammatory exudate or debris will demonstrate CT numbers in the soft-tissue range. In such instances, ultrasound can sometimes help clarify the fluid nature of the mass in question. If there is still doubt, needle aspiration using either CT or ultrasound guidance will generally settle the issue. Aspiration of pus can then be followed therapeutically by percutaneous placement of a flexible catheter for abscess drainage.

Another major use of CT in Crohn's and other inflammatory bowel diseases is to delineate accurately fistulae and sinus tracts. While such tracts can be demonstrated by means of conventional barium studies or fistulography, it is often difficult to determine by either method the total number, exact location, and full extent of these tracts. Scans obtained with contrast in the sinus or fistula are helpful in conceptualizing its configuration in three dimensions and in defining its spatial relationship to adjacent structures (1, 12, 14). Abscesses in unusual locations, such as the anterior abdominal wall, can be shown to result from underlying enteric fistulization (15).

Perirectal inflammation may result in significant pain and tenderness and so limit or preclude rectal administration of contrast material. This may also present a problem in evaluating peristomal recurrences. If properly timed, opacification of these areas by way of peroral contrast may be the best and sometimes only means of evaluating these patients. Periproctitis results in changes similar to those seen in the mesentery, that is, increased density to or proliferation of perirectal fat (Fig. 4). Fistulae and abscess formation can be identified and accurate assessment of the extent of the inflammatory process into the pelvis, to the pelvic side walls, or to the prostate, uterus and bladder is recorded (5).

Diverticulitis

Acute diverticulitis is a common cause of abdominal pain and fever in adults. While the clin-

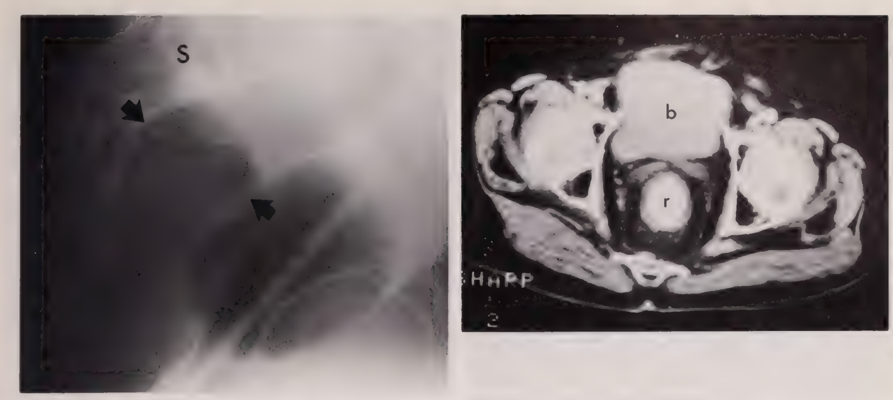


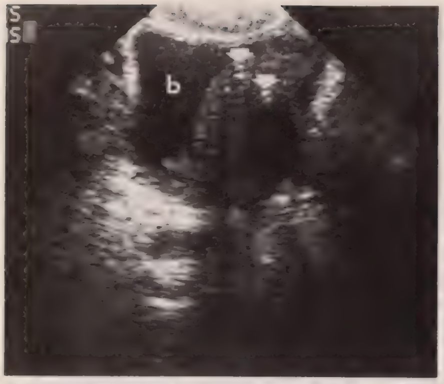
Fig. 4. **Left** Lateral coned-down film from barium enema on male patient with chronic Crohn's disease and previous perirectal fistulae; s = sacrum. Wide separation of rectum and sacrum (arrows) suggests possibility of presacral abscess. **Right** Contrast-enhanced CT scan through plane of midrectum after contrast enema. Mild circumferential and symmetrical thickening of rectal wall (r = rectum, b = bladder); abundant perirectal fat, especially between rectum and sacrum, accounts for barium enema findings. No abscess was found.

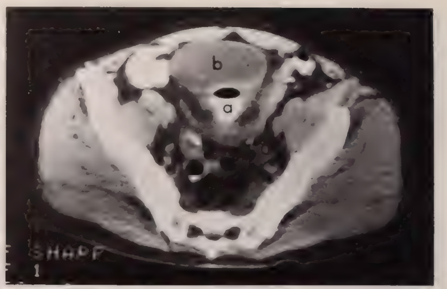
ical findings may be strongly in favor of this diagnosis, patients may present a nonspecific or confusing picture. In some such instances, ultrasound or CT are often requested before appropriate contrast studies. It may be possible to make the diagnosis if specific abnormalities are noted. More important, however, is the use of ultrasound or CT in evaluating the severity of disease in patients known to have acute diverticulitis, when it may be difficult to decide upon the optimal therapeutic approach. Surgery may be averted or postponed if there is evidence that inflammatory changes are limited with no findings to suggest perforation or abscess formation, frequent complications of severe diverticulitis which can be impossible to assess by other means.

The ultrasound findings in acute diverticulitis may be subtle or limited because of a large amount of intestinal gas near the involved segment of colon. Thickening of the bowel wall is much the same as in Crohn's disease. The presence of associated diverticula may be suspected by the demonstration of small echogenic foci, with acoustical shadowing representing air or retained barium within the diverticula. Involvement of the sigmoid colon without other sites of abnormally thick-walled bowel, especially in the right lower quadrant, would weigh more heavily in favor of diverticulitis than Crohn's. The sigmoid colon can be readily seen through the urine-filled bladder, especially when spasm, circular-muscle hypertrophy, and mucosal edema result in prominence of its walls and exclusion of interfering gas from its compromised lumen.

The proximity of the urinary bladder, vagina, uterus, seminal vesicles, and prostate to the sigmoid colon accounts for occasional involvement of these structures secondarily by inflammation. Air in the bladder, vagina, or uterus results in characteristic shadowing on ultrasound, suggesting fistulous communication with the colon if other causes, such as Foley catheterization or recent pelvic examination, can be excluded. Before such fistulization actually occurs, it may be possible to show inflammatory thickening of the contiguous wall of these structures.

Inflammation of the pericolic fat surrounding diverticulitis does not appear to incite as dramatic a fibrofatty proliferation as Crohn's disease; but in the acute phase of severe diverticulitis, a significant phlegmon may be present which, by physical examination or contrast enema, may be difficult to differentiate from diverticular abscess. Sometimes, typical sonographic findings of an abscess are found; however, some abscesses will go undetected because of overlying bowel gas or gas in the abscess masquerading as gas in the bowel. On the other hand, peridiverticular phlegmon may be so transonic and hypoechoic as to mimic an abscess. It is in cases such as this that contrast-enhanced CT is most useful (Fig. 5).





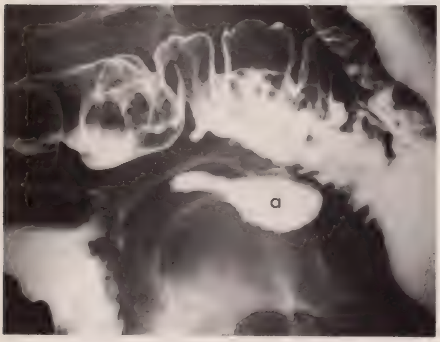


Fig. 5. Above left Transverse image from pelvic ultrasound in man with suspected diverticulitis. Urinary bladder (b) is indented by mass whose posterior border is difficult to demonstrate due to acoustical shadowing arising from collections of gas within mass (arrows). **Above right** Corresponding CT scan: extraluminal collection of contrast material and air (a) contiguous with thickened posterior wall of bladder (b). Increased density of perivesical fat behind bladder and to either side of this diverticular abscess. **Left** Barium enema after ultrasound and CT studies confirms presence of diverticular disease and abscess cavity (a).

Diverticula of the colon are quite obvious on CT when filled with air or contrast material since they project into and are usually well marginated by pericolic fat. When extensive diverticulosis is present, rows of these outpouchings can be seen running along the borders of the colon, whether or not there has been optimal distention of the bowel lumen. As already discussed, such distention is important for evaluating wall thickness, which may be increased even in the absence of acute inflammation, due to circular-muscle hypertrophy. The difference between this muscular thickening and the swelling which accompanies diverticulitis is generally one of degree and extent, and differentiation is, therefore, somewhat subjective. Nevertheless, diverticulitis most often results in changes in adjacent fat which are not found with uncomplicated diverticulosis.

As in Crohn's disease, the inflammatory reaction associated with diverticulitis causes a localized increase in the CT attenuation values of pericolic or mesocolic fat due to the outward spread of edema and reactive cells from the inflamed wall. This results in an ill-defined haziness to the fat surrounding the bowel. Engorged lymphatics or confinement of the inflammatory changes to established fascial planes probably accounts for the more discrete, fine, curvilinear, or streaky densities. Thicker linear densities crossing through the fat suggest fistulae or sinus tracts, which may or may not fill with contrast. Longitudinal submucosal fistulization can be demonstrated, and such findings correlate well with barium-enema findings (Fig. 6).

Diverticular abscesses have no unique features compared to those resulting from other causes, except for their consistent and intimate relationship to an abnormal-appearing segment of colon. The absence of orally or rectally administered contrast material within these abscesses does not rule out the possibility of narrow or intermittent communication with the bowel. As previously mentioned, differentiating a large area of phlegmon from abscess may be difficult by CT. It is important to be able to make this distinction since even extensive phlegmon can resolve with medical management (Fig. 7), whereas, a well-formed abscess must be drained for adequate treatment. Although the CT density of the contents of an abscess may be higher than that of

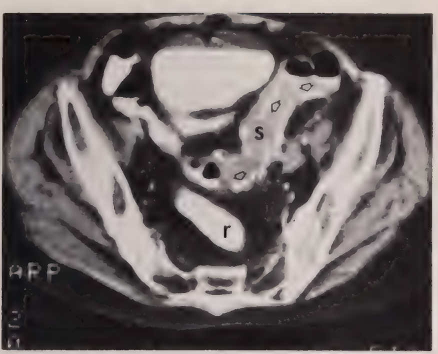


Fig. 6. Pelvic CT of woman, age 58, with known bladder carcinoma and lower abdominal pain. Marked thickening of walls of sigmoid colon (s); sparing of rectum (r). Lumen of this abnormal segment of colon was not demonstrated but contrast material can be seen tracking through multiple intramural longitudinal fistulae (arrows). Barium enema subsequently confirmed diverticulitis.

other fluid collections due to inflammatory debris or blood, intravenous contrast-enhanced scans often show a characteristic enhancement of the wall of the abscess, helping to distinguish it from phlegmon (Fig. 8).

Percutaneous CT or ultrasound-guided catheter placement for drainage of abscesses or other fluid collections are now well-established alternatives to surgical drainage in many situations (16–18). Drainage of pelvic abscesses can be challenging. Lateral or posterior approaches are limited by the bony pelvis, and finding a safe anterior approach is difficult because of the presence of low-lying small bowel loops, redundant segments of the sigmoid colon, and the urinary bladder, or uterus. For this reason it is preferable to use CT guidance or to at least choose an appropriate route for the catheter from a recent CT scan, regardless of the mode of insertion.

Appendicitis

The ultrasound and CT features of inflammation of the appendix closely resemble those of diverticulitis or Crohn's disease. While the appendix itself is not demonstrable by ultrasound and only occasionally seen by CT, the inflammatory response associated with appendicitis may result in thickening of the walls of the contiguous bowel, which can be shown by either technique. Localized phlegmon and edematous changes surrounding the appendix should be differentiated from abscess, a distinction which may be difficult by ultrasound alone, as previously discussed (Fig. 9).

In most instances, the diagnosis of appendicitis is made without the help of the radiologist. Plain film findings are usually nonspecific, unless a classic appendicolith is visualized. In cases where the clinical presentation is unusual, but in which appendicitis is one of the diagnostic considerations, a barium enema is often ordered. However, diagnostic ultrasound and CT may be requested before the administration of barium.

CT has proven itself useful in the diagnosis of appendiceal abscesses and associated complications, such as right ureteral obstruction or perinephric abscess. The extent of disease and its intraperitoneal versus extraperitoneal location, as

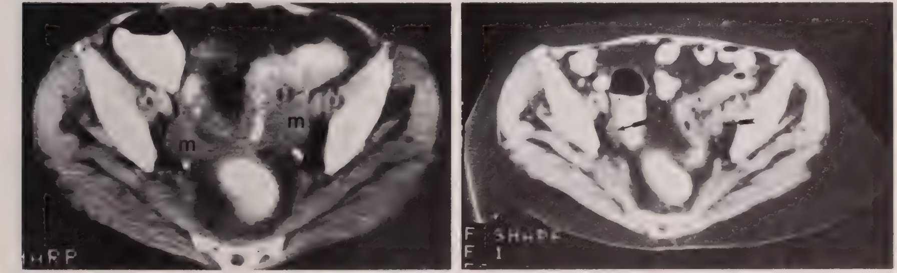


Fig. 7. Left At CT, 70-year-old woman with known ulcerative colitis had developed symptoms and signs of diverticulitis. Marked thickening of walls of sigmoid colon; two focal regions of increased density (m) adjacent to involved bowel just anterior to contrast-filled ureters. **Right** Following antibiotics, repeat pelvic CT shows resolution of bowel wall thickening and only small areas of residual pericolonic soft tissue density, which are presumed to represent resolving phlegmon or fibrosis (arrows).

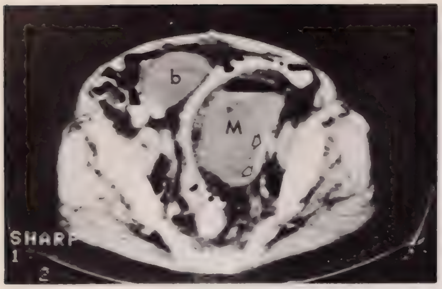


Fig. 8. CT of pelvis requested because of hypoechoic mass demonstrated on recent ultrasound in patient just "recovered" from bout of diverticulitis. Sigmoid colon is draped over large fluid-filled mass (M) on left side of pelvis. Density of mass is similar to that of urine-filled bladder (b); enhancing wall borders portion of mass (arrows).

well as its spatial relation to adjacent organs and vessels, are well depicted by CT (19, 20).

Other Inflammatory and Related Disorders

Extrinsic Sources. Inflammation of the bowel need not originate primarily in the colon or small intestine. Most CT and ultrasound findings already discussed are rather nonspecific. Like appendicitis any extrinsic inflammatory process can cause reactive thickening of the walls of adjacent cecum and terminal ileum. We have observed this in the pelvis in cases of advanced pelvic inflammatory disease (Fig. 10), and one should expect similar findings when any intraabdominal or retroperitoneal infection is in direct contact with the gastrointestinal tract. Involvement may also be found remote from a severe inflammatory process when inflammatory exudate extends along the length of a contiguous segment of bowel. This may be seen in acute pancreatitis, a condition in which it is common to observe by CT the spread of phlegmon along the left colonic gutter (5). Although resultant areas of altered echogenicity and CT density are predominately extraserosal, it is sometimes difficult to differentiate these changes from those affecting various layers of bowel wall or mucosa. The CT appearance of mesenteric, omental, or retroperitoneal fat is indistinguishable from its appearance in primary inflammatory bowel disease.

Endometriosis may involve some portion of the intestine in greater than 10% of cases. It usually affects the rectosigmoid but may also be seen involving the small bowel, cecum, or appendix. Findings on barium studies may mimic primary or metastatic malignancy or pelvic inflammatory disease. The CT findings are also nonspecific (21). Serosal implants can result in thickening of the wall of involved segments, and endometriomas may have ultrasound and CT characteristics that are virtually indistinguishable from those of abscesses.

Acute inflammation of the large or small intestine may also result from external or internal ir-

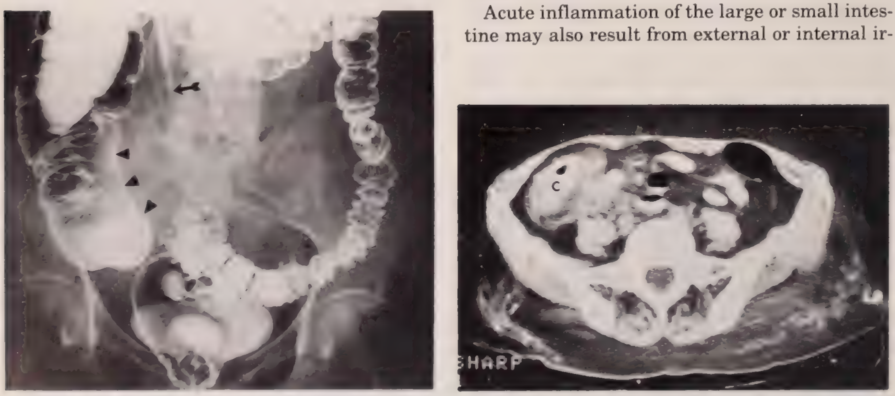


Fig. 9. Left Postevacuation film from a barium enema following intravenous pyelogram on a 77-year-old woman with chronic right lower quadrant pain. Extensive prior workups were negative, leading to psychiatric evaluation. Extrinsic pressure effect on cecum (arrowheads) and partial right ureteral obstruction (arrow) suggest large intraabdominal or retroperitoneal mass. Right Pelvic CT reveals prominent thickening in walls of cecum (c) and generalized increased density in right lower quadrant fat, accounting for mass effect on barium enema. Surgical specimen subsequently showed chronic typhlitis with transmural fibrosis and pericecal panniculitis and phlebitis.

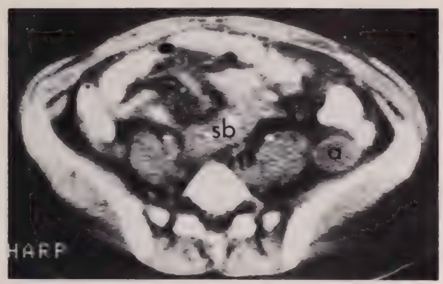


Fig. 10. Above left Pelvic CT of 39-year-old female diabetic with recent removal of an IUD, low-grade fever, and tenderness on pelvic examination. More caudal scans showed cul-de-sac and tubo-ovarian abscesses. Another small abscess (a) is present behind descending colon. Note haziness to mesenteric fat and abnormal small-bowel loop with thickened walls secondary to adjacent inflammation (sb).

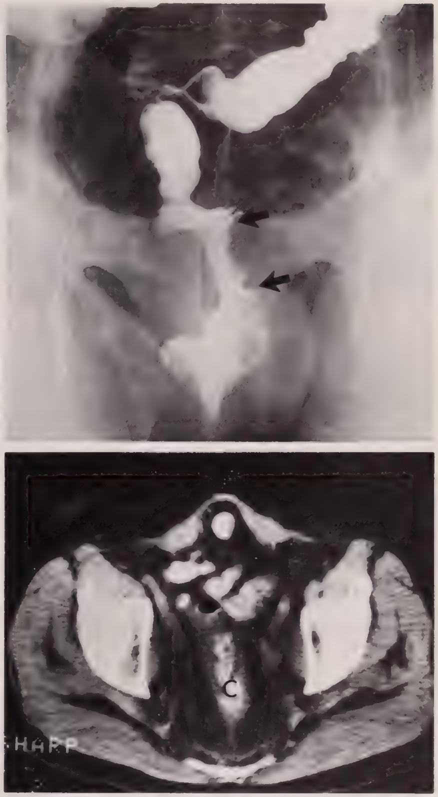


Fig. 11. Above right Following radical cystectomy for bladder carcinoma, this patient underwent radiation therapy to pelvis and subsequently had this barium enema because of constipation and low pelvic pain. A long segment of rectosigmoid shows poor distensibility, narrowing and irregular mucosa (arrows). **Right** Pelvic CT demonstrates some increase in perirectal fat density, widening of presacral space, and thickening of walls of involved segment of colon (c). Sigmoidoscopic biopsy was consistent with postirradiation changes; patient remains free of recurrent tumor one year later.

radiation. Radiation enteritis or colitis will thus be difficult to differentiate from Crohn's disease or diverticulitis on the basis of ultrasound or CT findings alone. Long-term effects, such as irreversible mucosal destruction or stricture formation, would not usually be detectable by either imaging modality; only a finding of dilated, fluid-filled bowel segments might be likely. By CT, chronic fibrotic changes in perirectal and pericolonic spaces or mesenteric fat are indistinguishable from acute inflammatory changes (Fig. 11).

Intrinsic Sources. Several pathologic inflammatory processes seem preferentially to involve the region of the cecum and terminal ileum, thus making differentiation from Crohn's disease difficult, even with conventional barium studies. Ultrasound and CT are also not helpful. These processes are relatively uncommon and include intestinal tuberculosis, amebiasis, and leukemic typhlitis. The latter, also known as ileocecal syndrome, is a necrotizing enteropathy occurring in children with acute leukemia and is characterized by inflammation of the cecum, appendix, and ileum, often associated with necrosis or perforation (22).

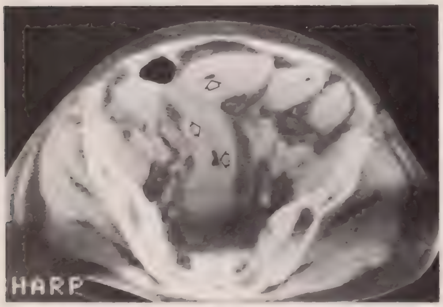
Since it is very often difficult to determine by ultrasound or CT which layer of the bowel wall or mucosa is responsible for abnormal thickening, any process which results in swelling of the mucosa or submucosa of either the small or large bowel may mimic the diseases thus far discussed. Nonspecific bowel-wall thickening has been seen in Whipples disease (23), pseudomembranous colitis (24, 25), amyloidosis (4), and with hypoproteinemia. Mucosal thickening and edema of the lamina propria resulting in the CT appearance of bowel-wall thickening has also been reported in association with villous hypertrophy of the small bowel in a patient with a glucagonoma (26).

Small and large bowel ischemia, anticoagulation, bleeding diathases, and trauma are associated with intramural intestinal edema and hemorrhage. In many instances there is also a significant ileus, and intestinal gas may hamper ultrasonic evaluation. Wall thickening can best be appreciated by CT in such cases (Fig. 12) and is a nonspecific finding, except in rare situations in which pneumatosis intestinalis or gas in branches of the portal venous system can be demonstrated. Extensive hemorrhage may extend beyond the walls of the affected bowel, resulting in ill-defined areas of increased CT density in the surrounding mesenteric and retroperitoneal fat, similar to the previously outlined inflammatory changes (Fig. 13).

Neoplasms

A major category of disease which must be included in the differential diagnosis when CT or ultrasound findings suggest inflammatory bowel disease is that of primary or metastatic tumors. Benign or malignant neoplasms are a common cause of localized bowel thickening detectable by either method. In addition, many malignancies involving the bowel wall are associated with changes extending into the surrounding mesenteric or retroperitoneal fat, most likely representing a combination of increased vascularity, lymphatic engorgement, or the direct spread of the tumor beyond the serosa. Occasionally, the extraserosal changes are indeed of an inflammatory nature, the result of intestinal perforation or fistulization (Fig. 14). In such a case, the diagnosis of malignancy may be masked by clinical and radiographic features more typical of an inflammatory process. If CT or ultrasound findings do not improve or show progression on follow-up examinations in the face of appropriate therapy for the presumed inflammatory bowel disease, underlying neoplasm should be suspected.

Lymphoma is a frequently encountered tumor that in its CT or ultrasound appearance may mimic inflammatory bowel disease (Fig. 15). Primary tumor, such as adenocarcinoma of the colon or small bowel, is generally limited to a short segment of intestine and thus may appear as a more focal mass (Fig. 16). Lymphoma, however, by virtue of its characteristic submucosal spread, results in a longer area of segmental wall thickening. By ultrasound, this results in a hypoechoic mass surrounding the more densely reflective musosa, just as in Crohn's disease, diverticulitis, and many of the other disease processes mentioned above. The CT findings are also nonspecific. Differentiation from Crohn's disease may be especially hard since the terminal ileum is most commonly involved and the cecum is the most frequent colonic site of involvement in both Hodg-



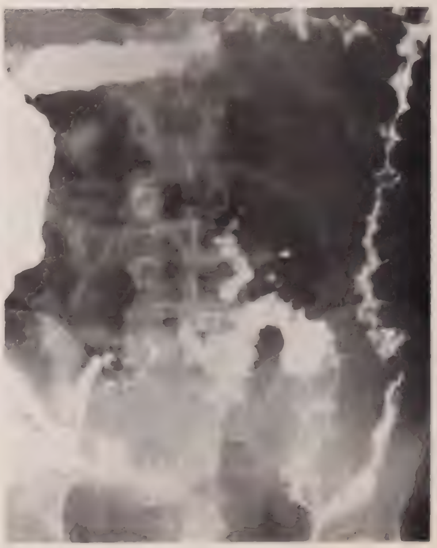


Fig. 12. **Above** Abdominal and pelvic CT was requested to rule out abscess in this patient with renal failure, hypotension, and leukocytosis. Marked thickening of colonic walls; small amount of fluid and air outlines narrowed lumen (arrows). **Right** Barium enema on this patient suggests ischemic colitis and intramural hemorrhage as evidenced by extensive thumbprinting of mucosa from midtransverse colon distally. This diagnosis was confirmed at autopsy.

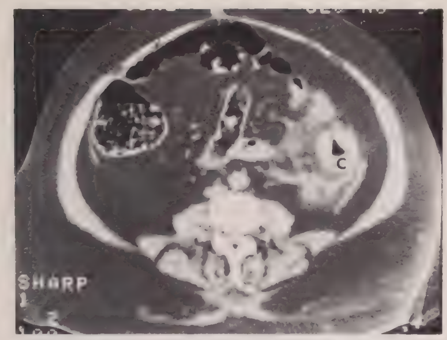


Fig. 13. Hemorrhage into walls of descending colon (c) occurred spontaneously during straining in this patient with thrombocytopenia of unknown etiology. Thickening of the bowel wall; bleeding extends into pericolonic retroperitoneal fat.

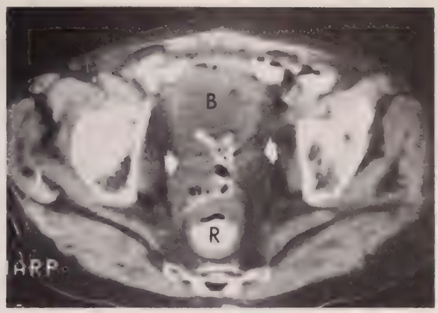


Fig. 14. Man, age 71, with three-month history of diarrhea and lower abdominal pain three years after surgery for colonic carcinoma. He recently experienced difficulty initiating good urinary stream without straining. A tract of extravasated contrast material and gas runs from rectum (R) anteriorly into urinary bladder (B) through fistula created by irradiation and recurrence of tumor (arrows).

kin's and non-Hodgkin's lymphomas, with concomitant involvement of the ileum in more than one-third of cases (27). Narrowing of the intestinal lumen can result in the string sign, generally associated with regional enteritis (9).

Asymmetrical thickening of the bowel wall is seen with serosal metastases from remote primary malignancies, mesothelioma, and in leiomyosarcomas originating in the GI tract. Such asymmetry may also be found in the exoenteric form of the intestinal lymphoma (3, 28). Although Crohn's disease, primary adenocarcinoma, and intramural hemorrhage usually result in circumferential and symmetric wall thickening, the demonstration of an exocentric lumen by CT or ultrasound cannot always be relied upon as a differentiating feature. The density-discrimination capability of CT may be helpful in diagnosing certain intramural mass lesions, such as lipomas, duplication cysts, or leiomyomas containing calcification (5, 29).

Carcinoid tumors of the intestine are submucosal lesions most often found in the appendix or ileum; they are the most common tumors of the small bowel. Associated muscular hypertrophy and fibrosis contribute to wall thickening indis-

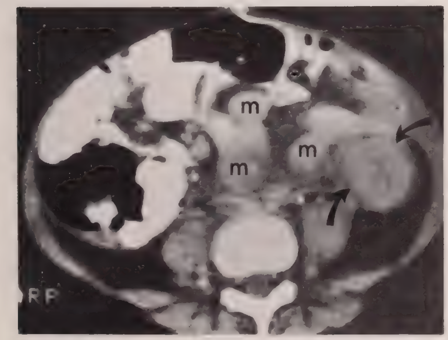


Fig. 15. Boy, age 7, with newly diagnosed lymphoma. Walls of descending colon (arrows) are markedly thickened due to lymphomatous infiltration; many small mesenteric masses represent lymphadenopathy (m).

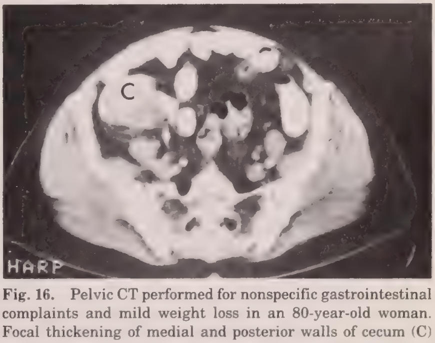


Fig. 16. Pelvic CT performed for nonspecific gastrointestinal complaints and mild weight loss in an 80-year-old woman. Focal thickening of medial and posterior walls of cecum (C) and two curvilinear densities in pericecal fat behind mass. Adenocarcinoma of cecum was proven by colonoscopy with biopsy.

tinguishable from other causes (30). Infiltration by the tumor and its desmoplastic reaction beyond the serosa may follow the pathways of lymphatic drainage and result in the CT findings of a soft tissue mass in the mesenteric fat, with irregular, spiculated margins aligned with the neurovascular bundles. Retraction of bowel loops toward the mass has been described as a characteristic finding (31); otherwise, the CT and ultrasound findings in carcinoid tumors resemble those of other neoplastic or inflammatory processes.

Summary

Inflammatory diseases of the large and small intestine result in a number of abnormalities which were predictable but not detectable until the development and refinement of cross-sectional imaging techniques such as ultrasound and CT. Direct visualization of the bowel wall and extraserosal fat make it possible to assess the extent of inflammatory or neoplastic processes and their effects on adjacent structures. While bowel wall thickening is common to a variety of diseases involving the gastrointestinal tract, discovery of such a finding on abdominal ultrasound or CT can offer an important clue to diagnosis in patients with nonspecific or confusing abdominal complaints. In patients known to have inflammatory bowel disease, ultrasound and especially CT can be instrumental in directing therapeutic management by documenting or excluding the presence of complications, such as abscess and fistulization. Ultrasound or CT-directed percutaneous needle aspiration of suspected abscesses is helpful in questionable cases and may be followed by nonoperative catheter drainage, using ultrasound or CT guidance. Serial studies may show resolution of abnormal findings in response to appropriate medical management or may instigate a change in treatment or reevaluation of the working diagnosis when stability or worsening of findings is demonstrated. Despite the strikingly similar changes seen in many noninflammatory disorders of the gastrointestinal tract, CT and ultrasound have proven to be useful ancillary studies in the workup, initial management, and follow-up of the patient with inflammatory bowel disease.

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Stomach and Duodenum

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Treatment of Gastrinoma

Robert M. Zollinger, M.D.

We honor the memory of a remarkable teacher of roentgenology, whose lucid observations clarified many previously unsolved problems of the gastrointestinal tract. Although his interests were primarily directed toward the small and large intestines, Richard Marshak was intrigued by the secondary effects of the gastrinoma on the upper small bowel and the stomach. In his book co-authored with A. E. Lindner, *Radiology of the Small Intestine* (1), one chapter was devoted to gastrinoma.

Roentgenologists played a significant role in raising early suspicions that islet cell tumors of the pancreas might be important in peptic ulcerations. In 1952, Forty and Barrett (2) described a possible relationship between changes in the third portion of the duodenum and the presence of islet cell tumors. Christoforidis and Nelson (3), in 1966, described the classic roentgenologic findings leading to the recognition of the gastrinoma syndrome. The roentgenologist is often the first to suggest the diagnosis of gastrinoma to the clinician, who confirms the suggestion by serum gastrin determinations and the secretin "push."

The gastrinoma syndrome is no longer a clinical novelty. It has become well known, and diagnosis can be confirmed by appropriate roentgen and laboratory studies, including gastric analysis and serum gastrin determinations supplemented by the secretin push. The gastrinoma is often small and multiple, with a tendency to metastasize. It tends to defy diagnosis by the usual scans unless it is large (one centimeter or more in diameter), and it resists visualization by angiography. Debas et al (4) have suggested heightened visualization of the gastrinoma by angiography when the secretin push is performed simultaneously with the angiographic procedure. Percutaneous venous sampling may be employed in the hope of accurately localizing a solitary gastrinoma, the removal of which will accomplish cure of the patient.

Since 1955, when we described the gastrinoma syndrome (5), several alternatives to the original recommendation of total gastrectomy and gross tumor excision have been suggested. Local excision of a solitary tumor of the pancreas or a solitary cardinoid-type gastrinoma in the submucosa of the first portion of the duodenum may result in a sustained reduction of the serum gastrin level to normal in 7% to 15% of patients. With earlier diagnosis and surgical intervention, the percentage of total tumor excisions should be increased, but surgeons hesitate to operate on the pancreas because of the fear of complications, and their medical colleagues often insist on years of medical therapy with the H_2-receptor antagonists before agreeing to a surgical exploration. Since 1976, the H_2-receptor antagonists have enabled physicians to control temporarily the symptoms associated with gastric hypersecretion. This led to the adoption of a conservative nonsurgical approach but the dosage of the H_2-receptor antagonists was slowly but surely increased as a tumor grew, until undesirable side effects resulted from heavy medication (6). Some failures were due to poor compliance with the medication regimen, and some patients did not respond favorably to the H_2-receptor antagonists.

A welcome return to earlier surgical intervention has been observed, owing to recently reported failure of long-term medical therapy (7). It is to be hoped that another prolonged delay will not take place while ranitidine, another H_2-receptor antagonist, is given various trials by those who are convinced that as long as gastric acid values can be reduced to below 10 mEq per hour by medication, this form of therapy is preferable to total gastrectomy and tumor resection. The

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gastrinoma is the only islet cell tumor not routinely treated surgically despite the fact that it is a malignant tumor with frequent metastases.

Vagotomy, which reduces the acid output to a level that can be more easily controlled by H_2-receptor antagonists, has been recommended instead of total gastrectomy. When no tumor is found at exploration or there is convincing evidence that all tumor has been excised, vagotomy and pyloroplasty may be occasionally recommended by the surgeon. However, he should have evidence of the patient's willingness to comply with the prescribed medication regimen. In addition, he should have laboratory evidence that a reasonable dose of an H_2-receptor antagonist will reduce the patient's acid output to below 10 mEq per hour. When a procedure other than total gastrectomy is considered, surgeons may find supporting evidence for the lesser procedure; however, most surgeons experienced in the treatment of patients with gastrinoma continue to consider the original recommendation of total gastrectomy, with Roux-en-Y reconstruction and excision of as much gross tumor as is safely possible, to be most conducive to long-term, symptom-free survival.

While the diagnosis of gastrinoma may now be made more frequently and earlier in the course of the disease, such gains can be lost by prolonged nonsurgical treatment to control the hormonal effects of such tumors on the stomach. After almost 30 years, it is time to routinely consider the gastrinoma a surgical problem. For the best results, patients with this relatively uncommon tumor should be treated only by surgeons familiar with endocrine surgery who are also competent to perform total gastrectomy, hemipancreatectomy, or local extirpation of a gastrinoma. Local excision of gastrinoma from the head of the pancreas seems more desirable than a Whipple procedure, since residual small tumors in the remaining pancreas would most likely continue to produce gastric hypersecretion with recurrent ulceration.

Wemer (8) recognized the multi-endocrine adenomatosis syndrome in 1954. It is becoming clear that the gastrinoma is commonly associated with hyperparathyroidism in 20% to 25% of patients. Unless three and one-half parathyroid glands are removed, the tendency is for hyperparathyroidism to recur over the years. Hyperparathyroidism should be corrected some time before abdominal exploration for the gastrinoma is undertaken.

Prolactinomas are not uncommonly associated with gastrinomas and may be disclosed in the children of patients with MEN I. Prolactin levels, if elevated, need to be repeated, and computed tomography scans of the pituitary fossa should be made (9). Transphenoidal removal of the microadenoma of the pituitary may be indicated.

While pheochromocytomas are considered a part of the MEN II syndrome, we have observed that these tumors are associated with gastrinoma in approximately 10% of all patients with proved gastrinoma. A yearly endocrine survey including scans of the pancreas, liver, adrenals, and pituitary fossa is worthwhile, especially in patients with MEN I, since secondary endocrine tumors may be verified years after a gastrinoma has been detected. The children of these patients should have at least one endocrine survey.

It is impossible to predict the clinical course of a patient with gastrinoma. One of the patients described in our original report in 1955 has had two children and is working every day, almost 30 years after undergoing total gastrectomy. Approximately 50% of our patients survived 10 years or longer. Their total preoperative and postoperative clinical history may well exceed 15 to 20 years. Neither the gastrin levels, the microscopic examination of resected tumor, nor the extent of tumor including metastases to the liver provides reliable information for or against prolonged survival. Chemotherapy may be used and appears to benefit some patients, but kidney function must be carefully monitored.

The roentgenologist can be helpful in the follow-up evaluation of these patients, whose nutrition has been surprisingly good after total gastrectomy. Stenosis of the esophagojejunal anastomosis, gallstones, kidney stones, other endocrine tumor activity, metastases to the liver, or encroachment by tumor on the small intestine and other structures may be responsible for a myriad of postoperative complaints.

The pancreas is indeed growing less mysterious than it used to be in former years. But, it is critical to recognize that the gastrin-producing islet cell tumor is a solid, malignant tumor that grows inexorably each year.

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Snail-Like Spiral Deformity of the Stomach (Schneckenförmige Einrollung)

CHARLES H. LU, M.D., JAMES OLSON, M.D., AND EDMUND A. FRANKEN, M.D.

In 1911, Schmieden described a characteristic deformity of the stomach which he named schneckenförmige Einrollung, or snail-like spiral deformity. This is characterized by marked contraction and foreshortening of the lesser curvature of the stomach. Although recognized by the Japanese, few subsequent articles in the Western literature allude to this deformity, and none describe the symmetric lesser-curvature ulcer or scar as the most frequent cause. We present three patients who demonstrate this deformity, all with symmetric (linear or kissing) perpendicular ulcerations or scars across the lesser curvature.

Case 1. In 1970, a 59-year-old man was hospitalized with melena, anorexia, and syncope. He had a history of radiographically documented ulcer disease dating back to 1957. Stools were guaiac positive. An upper gastrointestinal series demonstrated a "large antral gastric ulcer" (films not available). He improved on medical management, was discharged, and was lost to follow up.

In 1981, the patient returned with anorexia and a 50-pound weight loss. A guaiac-positive stool was discovered. The upper GI series revealed a linear niche perpendicular to the long axis of the stomach and running across the lesser curvature, with resultant severe foreshortening of the lesser curvature. The pylorus and duodenal bulb were elevated and brought to lie adjacent to the incisura angularis, showing the snail-like spiral deformity and a linear niche perpendicularly across the lesser curvature (Fig. 1). Despite 12 hours of fasting prior to the examination, residual food was present in the stomach, suggesting partial gastric-outlet obstruction.

Subsequently, the patient was also diagnosed as having squamous cell carcinoma of the lung. He refused all therapy and was discharged.

Case 2. A 53-year-old woman, with a prior history of peptic ulcer disease, was hospitalized in 1975 with progressive right lower quadrant pain, hypochromic microcytic anemia, and guaiac-positive stools. An upper gastrointestinal series revealed an active linear ulcer at the antrum perpendicular to the lesser curvature and shortening of lesser curvature (Fig. 2). After medical management failed, the gastric ulcer was surgically removed from the lesser curvature. The operative note stated that the wound was closed across the lesser curvature and perpendicular to its long axis. Thus, a lesser-curvature transverse scar was surgically created.

In 1981, the patient was readmitted suffering from early satiety, epigastric pain, nausea, and vomiting. At endoscopy neither the pylorus nor duodenal bulb was identified. An upper gastrointestinal series revealed a large linear scar across the lesser curvature and a characteristic snail-like spiral deformity (Fig. 2). Although surgical consultants recommended surgery for partial gastric-outlet obstruction caused by this deformity, the patient declined.

Case 3. In 1970, a 58-year-old man was admitted to the hospital with complaints of epigastric pain, bloating, and occasional vomiting. He had an 11-year history of peptic ulcer disease, and, in 1959 and 1966, small ulcers had been diagnosed by x-ray at the gastric angle of the lesser curvature. Physical examination revealed epigastric tenderness and a succussion splash. Stools were guaiac positive and there was a hypochromic microcytic anemia. An upper gastrointestinal series revealed a linear ulcer across the lesser curvature, and the snail-like spiral deformity. Endoscopy confirmed the linear ulcer on the lesser curvature. The patient was discharged on medical therapy.

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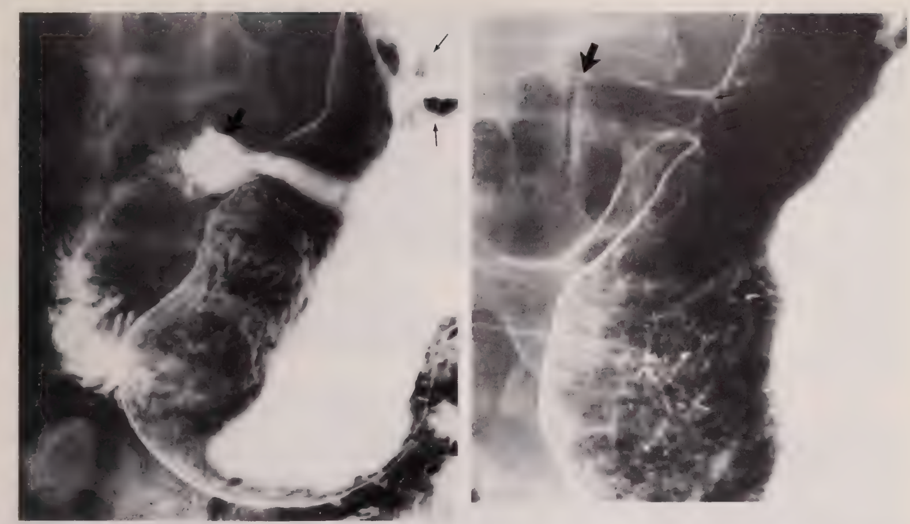

Fig. 1. Case 1. **Left** Snail-like spiral deformity with characteristic severe foreshortening of lesser curvature, resultant elevation of pylorus and duodenal bulb (large arrow), and relative elongation of greater curvature, causing pouchlike deformity of antrum. Notice food retention in gastric lumen (small arrows). **Right** Double-contrast study demonstrates linear niche (small arrows) perpendicularly across lesser curvature. Duodenal bulb (large arrow).

Discussion. Schneckenförmige Einrollung, or snail-like spiral deformity of the stomach, is characterized by marked contraction and foreshortening of the lesser curvature (1–3). This severe foreshortening results in elevation of the pylorus and duodenal bulb such that they lie in close approximation to the incisura angularis. There is also relative elongation of the greater curvature which results in a pouchlike deformity of the antrum (Figs. 1, 2). This deformity is likened to a snail, with the pouchlike antrum representing the mollusk's shell and the duodenal bulb representing its head (Fig. 3).

In all three of our cases, this deformity was caused by a linear scar or ulceration occurring perpendicularly across the lesser curvature. Generally, linear niches have been considered as a stage of or the result of healing of round or oval ulcerations of the stomach (2). However, Murakami (4) demonstrated that these linear lesions were most often active ulcerations themselves, and not just scars or a stage of ulcer healing. In minute pathologic studies, he showed that 97% of an unspecified number of patients thought to have linear scars actually had active linear ulcers or round ulcers. Furthermore, his pathologic sections showed these linear ulcers to be associated with fibrosis and retraction capable of producing severe lesser-curvature shortening. Shirakabe et al (5) reported a close relationship between the length of the linear ulcer and the degree of shortening of the lesser curvature.

In 1952, Hinds (6) described ten patients with gastric deformities similar to those described by us here. His extensive work demonstrated that lesser-curvative gastric ulcers could result in severe shortening of the lesser curvature. He postulated two factors as responsible for this type of deformity: "intrinsic shortening of the lesser curvature; and fibrosis and shortening of the gastrohepatic omentum." Although he did not note the transverse nature of the ulcer as frequently being the cause of the severe lesser-curvature fibrosis and shortening, he did describe one case as having a "saddle" ulcer, which he defined as "ulcer pockets remaining anteriorly and posteriorly, whilst healing had taken place with cicatrisation on the lesser curvature." This is the description of a transverse symmetric ulcer.

In 1969, Masuda (7), in the Japanese literature, reported his study of forty surgical patients whose stomachs had the snail-like spiral deformities. Most (82.5%) of these deformities were caused by symmetric ulcers (55% transverse linear ulcers,

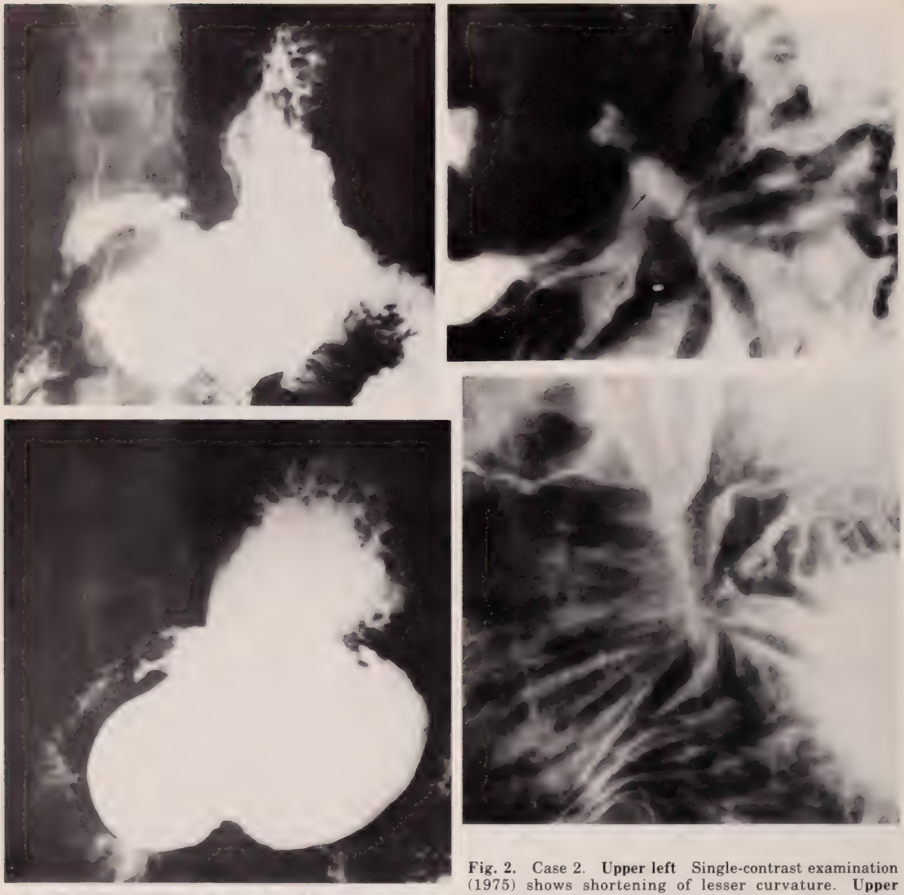

Fig. 2. Case 2. **Upper left** Single-contrast examination (1975) shows shortening of lesser curvature. **Upper right** Spot film (1975) indicates round lesser curvature ulcer at apex of linear mucosal niche (arrows). **Lower left** Characteristic snail-like spiral deformity with forshortened lesser curvature, elevated pylorus and bulb, and pouchlike antrum (1981). **Lower right** Double-contrast examination (1981) of lesser curvature clearly demonstrates linear scar with radiating mucosal folds.

27.5% kissing ulcers). The remaining 17.5% were caused by either a single, giant gastric ulcer or multiple gastric ulcers of the lesser curvature. Shirakabe (8) and Kumakura (2) each described one case in which an infiltrating antral carcinoma caused a similar deformity but without linear ulceration.

As demonstrated by our three cases and the studies of Masuda (7), the symmetric transverse ulcer with associated fibrosis or scar of the lesser curvature is the most common cause of the snail-like spiral deformity of the stomach. Less often, penetrating ulcer scars and adhesion from previous penetrating ulcers or antral carcinoma can produce such an appearance (6–8). Therefore, radiographic demonstration of the transverse ulcer is the clue to accurate diagnosis. The deformity itself is easily diagnosed by either single- or double-contrast techniques. However, the double-contrast examination is needed to demonstrate the linear niche (5). The ulcer or scar can easily be recognized by the convergence of gastric folds

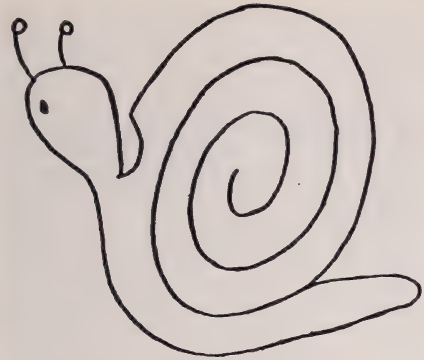

Fig. 3. Schneckenförmige Einrollung: snail's shell likened to antrum, head to duodenal bulb.

to a linear niche (5, 9) and has been described as having the appearance of a centipede (10) (Fig. 2).

In our three cases, the linear niches were easily demonstrated by the double-contrast examination. Since gastric outlet obstruction is a possible complication of this deformity, gastric retention of food or secretions may interfere with the barium coating. Therefore, it is necessary to use at least 200 ml of high density barium (240% w/v). Also, the stomach must be sufficiently distended with air, so that the linear niche is more easily outlined.

The recognition of the snail-like spiral deformity is important for several reasons. As demonstrated by two of our cases, it may be responsible for partial gastric-outlet obstruction (6, 10). The deformity itself serves as an indirect sign of peptic ulcer disease—this disease must be differentiated from antral carcinoma which may, although rarely, cause a similar appearance (2, 6, 8). Finally, it is helpful for the endoscopist to be aware of this deformity and its significance in order to achieve successful endoscopy.

Summary. We have described three patients in whom linear ulcers or scars have occurred perpendicularly across the linear curvature. This results in severe foreshortening of the lesser curvature, with a characteristic snail-like spiral deformity of the stomach. The double-contrast examination is ideally suited to demonstrate the lesser-curvature linear niche.

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Single-Contrast and Double-Contrast Radiography in the Detection of Gastritis

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The introduction of endoscopy with biopsy has eliminated some of the problems previously encountered in diagnosing gastritis, but confusion still exists as to the classification of gastritis. This confusion is related partly to the fact that some of the inflammatory gastric changes seen by the endoscopist (for example, congestion, erythema, and punctate submucosal hemorrhage) frequently are not identified by the pathologist because the histology is normal or fails to reveal a microscopic change that corresponds to the gross findings. This may result from sampling problems or the fact that some gross patterns of injury seen during light endoscopy are not represented by conventional histologic inflammation. Care must be taken not to attribute every change observed by endoscopy to gastritis. Often structural or functional markers of injury are needed. Another problem is that many patients with gastritis are not symptomatic. This is well known for erosive gastritis related to salicylates, particularly in patients with rheumatic disease or burns (1–4).

Radiography generally is considered to be of limited use for evaluating patients with gastritis (5). While the single-contrast technique of barium examinations in the upper gastrointestinal tract accurately demonstrates changes in which the surface of the gastric mucosa and the contour of the stomach are markedly altered (6–10), the double-contrast technique can detect smaller changes in the mucosal surface (11–15). The use of the latter technique, therefore, should improve diagnostic accuracy in patients with suspected gastritis.

In the following paragraphs, the endoscopic and radiographic manifestations of gastritis are related to one another, the diagnostic accuracy of each technique is determined, and the role of the modalities assessed.

Gastritis

Etiology and Symptoms. Many patients with gastritis are asymptomatic, making definite diagnosis difficult. More than 50% of the population over age 40 may have both antral and fundal gastritis (16).

Antral gastritis is more frequent and more severe than fundal gastritis. The lesser curvature often is more severely affected than the greater curvature, and the extent and severity of the nonspecific, nonerosive gastritis increase with age, an important consideration in making a correct diagnosis.

In a study we undertook in 68 patients with gastritis, we found no symptoms in 10 patients (17). The medical literature reports that bleeding is seen in up to 30% of patients (18). This was confirmed in our study, in which one-third of the afflicted patients presented with bleeding. Other symptoms are epigastric pain or discomfort, anorexia, nausea, and vomiting.

Acute gastritis may be seen after ingestion of alcohol, aspirin, or other anti-inflammatory drugs, or during chemotherapy. It also may be found after stress related to shock, severe trauma, operation, or infection, or it may follow gastric freezing, uremia, gastric irritation, staphylococcus food poisoning, or bile reflux after partial gastric resection. Aspirin and alcohol are the

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most common causes of gastritis, and although both may produce diffuse gastritis, they differ in that aspirin usually produces a distal gastritis, while alcohol usually causes inflammatory changes in the distal or proximal stomach. Stress gastritis is seen more often in the fundus and body of the stomach, and the changes are thought to be related to ischemia.

Gastritis, whether detected by radiography or endoscopy, is not always clinically relevant. In our study, gastric changes were considered a major clinical problem in 36%, an associated clinical but important problem in another 42%, and an incidental finding without any clinical significance in 32% of the patients (17). Treatment was changed for 62% of these patients because of the radiographic diagnosis of gastritis.

Classification. Before one can relate endoscopic to radiographic findings, one must decide on a workable classification of gastritis. Most classifications distinguish between acute and chronic changes. Some classifications are based on endoscopic appearance, some on the pathologic or histologic appearance, and some on practicalities such as patient treatment.

One widely used classification (5) is based on endoscopic appearance of the disease, and its subgroups are derived from the most prominent inflammatory changes in each category. These subgroups include superficial hemorrhagic and erosive gastritis for the acute gastritis group and chronic superficial, atrophic, granulomatous, eosinophilic, and hypertrophic gastritis for the chronic forms. Many clinicians use the descriptive terminology but also add a grading of mild, moderate, and severe. Infectious and corrosive types of gastritis belong to the group of acute gastritis, but usually are treated as a separate subgroup because the changes in these disease processes are much more severe.

Many classifications of gastritis bear no close correlation to radiographic findings. We therefore recommend the use of a different classification, that of Weinstein (16), which does not distinguish between acute and chronic changes. The terms "acute" and "chronic" often are confusing because many clinicians think of these terms as connoting a temporal quality of the disease, whereas for the pathologist, the term "acute" refers to a microscopic inflammation with prominent polymorphonuclear leukocytes and the term "chronic" refers to microscopic inflammation with prominent plasma cells and lymphocytes. The term "acute" may refer to the abruptness of onset of the disease or to its evanescence, or to both, as in many patients with burns or serious illness ("stress" lesions). Changes, on the other hand, may be "chronic" or perpetuated from a temporal point of view, as in patients with persistent or recurrent erosive gastritis without associated risk factors, in patients under aspirin therapy, and in alcoholics.

Weinstein's classification distinguishes specific and nonspecific gastritis and recognizes two subgroups in each category:

- erosive/hemorrhagic
- nonerosive

Specific types of gastritis may arise from tuberculosis, sarcoidosis, eosinophilic processes, opportunistic infection, hypertrophic processes, granulomatous processes, or diseases of proximal small bowel.

Endoscopy and Histology

In general, biopsies are not obtained in patients with erosive gastritis unless a specific cause for gastritis, such as Crohn's disease or opportunistic infection in an immunocompromised host, is suspected. The diagnosis of erosive gastritis is therefore based on the endoscopic appearance of the stomach. Erosions are defined endoscopically as shallow depressed areas of the mucosae which are small and usually multiple. Ulcers are larger but also appear as depressed areas of mucosa with exudate. Because of the similar appearance, ulcers and erosions frequently are confused with one another. According to Weinstein's classification (16), erosive gastritis is diagnosed if multiple erosions, which do not penetrate the gastric muscularis mucosae, are seen during endoscopy (16, 19). These erosions frequently are associated with inflammatory changes, and histological examination of biopsy specimens shows infiltrates of multiple polymorphonuclear leukocytes. Hemorrhagic gastritis, which is the hemorrhagic variant of erosive gastritis, is diagnosed endoscopically if either multiple punctate areas of hemorrhage or a diffusely bleeding friable mucosa is present (20).

Diagnosis of nonerosive, nonspecific gastritis is based primarily on histologic evidence. The three recognized subgroups of nonerosive, nonspecific gastritis are superficial gastritis, atrophic gastritis, and gastric atrophy. Superficial gastritis is characterized by inflammatory cells that are confined predominantly to the lamina propria near the gastric pit region. The gland zone is intact in these cases. Atrophic gastritis is diagnosed histologically if infiltrates of inflammatory cells into the gland zone and loss of glands of variable degrees are seen (16). Inflammatory cells may extend down to the muscularis mucosae. Endoscopically, atrophic gastritis is characterized by a pale mucosa with a shiny surface and a prominent submucosal pattern of vessels (21, 22). In all of these subgroups, intestinal metaplasia may be present with intestinal goblet cells, but metaplasia is more extensive in severe nonerosive, nonspecific gastritis. In atrophic gastritis, "antralization" of the gastric mucosa in the fundus may occur and clear-staining mucosal glands may be seen in that area.

Arbitrarily, histologically confirmed gastritis is defined endoscopically as mild, moderate, or severe. Mild gastritis is diagnosed if congestion and submucosal hemorrhage are seen during endoscopy. Moderate gastritis is diagnosed if friability is marked and/or some erosions are present. Severe gastritis is diagnosed if diffuse mucosal bleeding is present and/or multiple erosions are seen. Such a grading cannot be made radiographically for correlation to endoscopic grading because some of the endoscopic changes are too superficial or do not have a radiographic equivalent, as is the case for friability of the mucosa.

Radiography

Most patients with gastritis who are examined radiographically have a mild form of the disease. Very few patients with severe gastritis are examined radiographically because patients with severe gastritis often present with acute bleeding (19) and undergo endoscopy initially after stabilization. Most of these patients, therefore, are not candidates for radiographic examination when their gastritis is in the acute state. Because treatment is instituted immediately, these patients often undergo single-contrast or double-contrast examinations only after several days of treatment for gastritis, and the acute inflammatory changes are then less severe.

The present discussion is limited to nonspecific gastritis. We suggest, radiographically, only two subgroups of nonspecific gastritis should be distinguished: nonerosive and erosive. In our group of nonerosive types of gastritis, gastric atrophy and (rarely) atrophic gastritis was recognized radiographically (17).

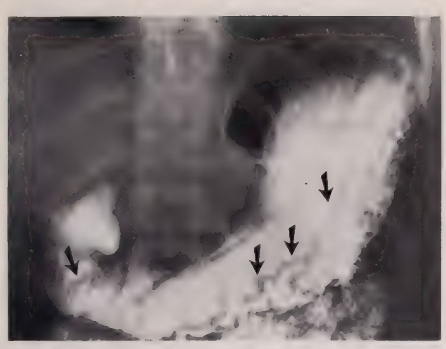
The radiographic diagnosis of nonspecific gastritis can be made if erosions are seen in the stomach, or if at least two of the following radiographic features are present: narrowed lumen; abnormal gastric folds; serrated, flattened, or crenulated margins; polypoid filling defects; and abnormal (coarse) areae gastricae.

Erosive nonspecific gastritis can be diagnosed radiographically only if erosions with or without other features suggesting gastritis are identified. The radiographic diagnosis therefore is based on a subjective impression using these radiographic signs as indicators. In a well-distended stomach, rugal folds that are scalloped or nodular are diagnosed as abnormal in any part of the stomach. Persistence of rugal folds in the antrum despite adequate distention of the stomach should be considered abnormal regardless of their appearance. Serrated margins are characterized by very small irregularities of the gastric walls, and crenulated margins are characterized by larger undulating margins. The areae gastricae are determined to be abnormal if they present with a "coarse" pattern, which is defined as an irregular, meshlike, nodular or polypoid pattern with nodular segments measuring more than 4 mm in diameter. A prominent areae gastricae pattern that consists of smooth and nonenlarged segments should not be considered abnormal.

In our investigation (17), the sensitivity of the double-contrast technique for detecting gastritis was higher than that of the single-contrast method for both types of gastritis (erosive/hemorrhagic nonspecific gastritis and nonerosive nonspecific gastritis). The difference in the respective sensitivities of the two methods was largest for detecting atrophic gastritis: 43% for single-contrast examinations and 83% for double-contrast examinations. The sensitivity for detecting erosive/hemorrhagic gastritis was 55% for single-contrast examinations and 68% for double-contrast examinations. Among the 4 patients with atrophic gastritis, lack of distensibility of the stomach ("tubular stomach") was observed in only one patient by each method, but abnormal thin folds were seen in 2 patients by the single-contrast method and in 3 patients by the double-contrast method.

For the single-contrast technique, narrowing of the lumen and abnormal margins were the least useful radiographic signs based on our study. For the double-contrast technique, abnormal folds in the body and/or fundus of the stomach and coarse areae gastricae patterns were the least useful radiographic features.

Demonstration by both the single- and double-contrast techniques of thin folds was specific for atrophic gastritis, but the number of patients in that group was too small for a definitive analysis. Lack of demonstration by the double-contrast



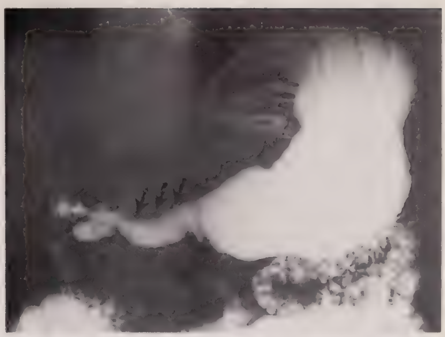
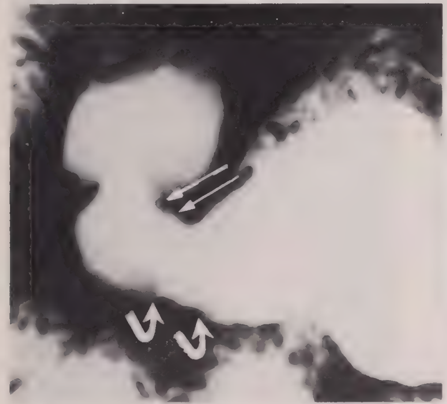


Fig. 1. **Left** Single-contrast examination of stomach shows narrowing of antrum and persistent nodular folds (arrows) in patient with nonerosive, nonspecific gastritis.

Fig. 2. **Right** Single-contrast method demonstrates narrowing of lumen and flattened, irregular margins (arrows) in patient with nonerosive, nonspecific gastritis. Reprinted, with permission, from Thoeni RF et al (17).

technique of polypoid filling defects in the antrum was specific for nonerosive, nonspecific gastritis. The remaining radiographic features demonstrated by both techniques were not specific for any particular type of gastritis. The radiographic features for erosive and, to a lesser degree, also for atrophic gastritis could be closely correlated to the endoscopic picture. Also, the absence of nodular filling defects in the antrum correlated well with the endoscopic picture of nonerosive, nonspecific gastritis.

When the radiographic features of abnormal folds, serrated, crenulated or flattened gastric margins, narrowing of the lumen, abnormal areae gastricae, polypoid defects, and erosion were analyzed in the correctly diagnosed cases of gastritis in our study, it was found that only 7% of the diagnoses were based on one single feature, 36% were based on 2 and 36% were based on 3 features, 18% were based on 4 features, and 3% were based on 5 or more features. For the single-contrast method, abnormal folds (Fig. 1), flat-



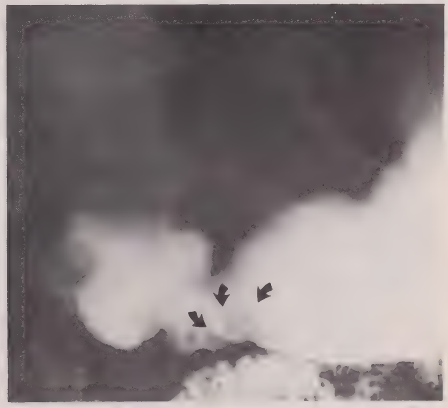


Fig. 3. **Left** Single-contrast examination shows markedly narrowed antrum with flattened and crenulated margins (straight arrows) and several polypoid filling defects (curved arrows). Patient suffered from moderate erosive nonspecific gastritis.

Fig. 4. **Right** Single-contrast technique clearly shows polypoid filling defects (arrows) in this patient with severe erosive nonspecific gastritis. Erosions are not identified without compression views. Reprinted, with permission, from Thoeni RF et al (17).

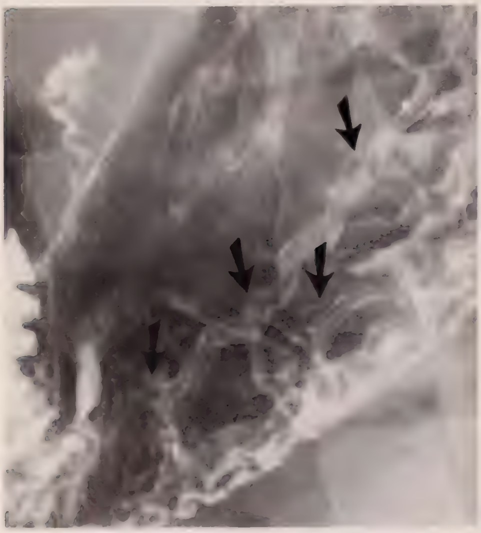
TABLE
Incidence of Radiographic Features of Gastritis by Single-Contrast and Double-Contrast Examinations

Features	Incidence (%)			
	Gastritis		Normal Stomach	
	SC	DC	SC	DC
Abnormal folds	24	37	11	28
Margins serrated	22	14	22	13
Margins flattened	8	3	0	0
Crenulated margins	22	15	24	4
Narrowing of lumen	39	29	30	11
Areae gastricae abnormal	1	12	0	13
Polypoid defects	7	10	2	2
Erosions	4	30	0	4

Reprinted, with permission, from Thoeni RF et al. Detection of gastritis by single and double-contrast radiography. Radiology 1983; 148:621–626.

tened margins (Fig. 2), polypoid defects (Figs. 3, 4), and erosions are useful radiographic features and lead only rarely to false-positive results (Table). When complete distention of the stomach cannot be achieved, false-positive results occur based on these two features. If polypoid defects and erosions are identified, the diagnosis of gastritis can be made correctly in almost all instances. Erosions become visible on spot radiographs of the single-contrast technique only when compression is used. However, nodular defects and erosions were only seen in moderate and severe types of gastritis. Like many other authors (14, 23) we found that the erosions detected usually were of the complete or varioliform type.

For the double-contrast technique, narrowing of the lumen, crenulated margins, polypoid defects, and erosions are useful features and lead only rarely to false-positive results (Table). With the double-contrast technique, false-positive results are obtained using nodular folds (Fig. 5), crenulated margins (Fig. 6) and narrowing of lumen, however, if complete distention cannot be achieved, or if the small bowel obscures the area of interest. The most useful radiographic signs of the double-contrast examination are erosions and polypoid defects (Figs. 7–10), representing mucosal elevations with or without central depressions and/or erosions (24). These defects usually occur in clusters in the antrum, but occasionally



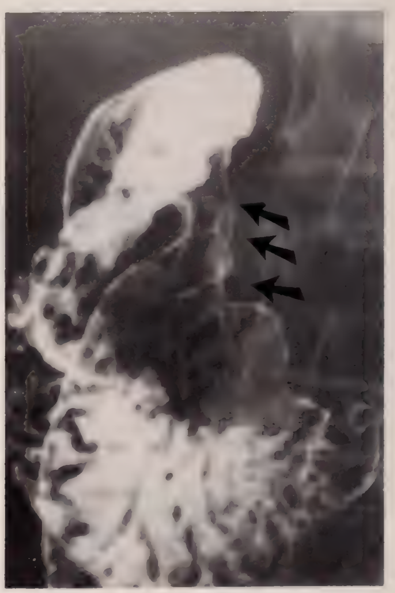
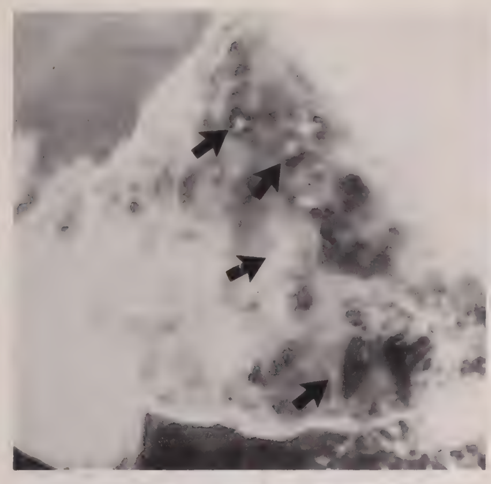
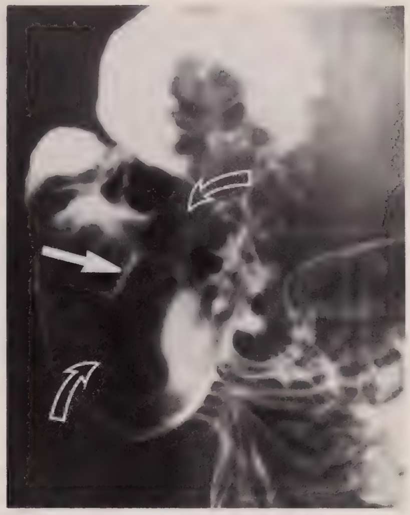
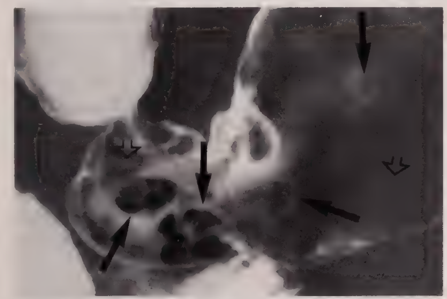


Fig. 5. Left Double-contrast examination shows scalloped folds (arrows) that persist during the entire examination in the presence of good distention. The patient suffered from nonerosive, nonspecific gastritis. Scalloped or nodular folds frequently lead to false positives.

Fig. 6. Right Double-contrast examination shows crenulated margins (arrows) in patient with nonerosive, nonspecific gastritis of moderate degree.







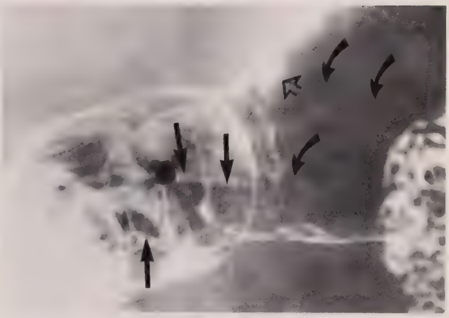


Fig. 7. Upper left Multiple punctate erosions (arrows) are present in the double-contrast examination of a 12-year-old boy with aspirin-induced erosive nonspecific gastritis.

Fig. 8. Upper right Nodular filling defects (curved arrows) and a linear ulcer (straight arrows) are identified in this patient with erosive nonspecific gastritis in the antrum.

Fig. 9. Lower left Multiple nodular filling defects (straight arrows) related to granulation tissue are seen in this patient with erosive nonspecific gastritis. Some of the nodules show central erosions (open arrows).

Fig. 10. Lower right Multiple erosions (curved arrows) and nodular filling defects (straight arrows) are easily seen in this patient with erosive nonspecific gastritis. A hyperblastic polyp (open arrow) also is identified.

they are seen in the body or fundus of the stomach. Rarely lymphoid hyperplasia of the stomach may be confused with the polypoid filling defects related to gastritis (25). False-positive results based on these two features occur only if coating is impaired or if distention is incomplete (Fig. 11). The appearance of the gastric folds often is not a reliable feature, and many false-positive results related to this feature occur solely because of technically unsatisfactory distention of the stomach. False-positive findings based on narrowing of the lumen and of normal gastric margins also are frequently related to incomplete distention of the stomach.

It is generally accepted that a coarse pattern of the areae gastricae (Figs. 12, 13) is a good indicator of the presence or absence of gastritis (26, 27). One study (28) was able to demonstrate a

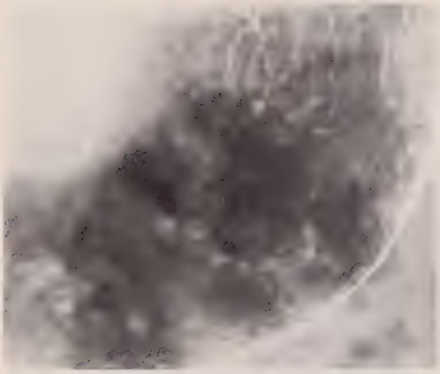
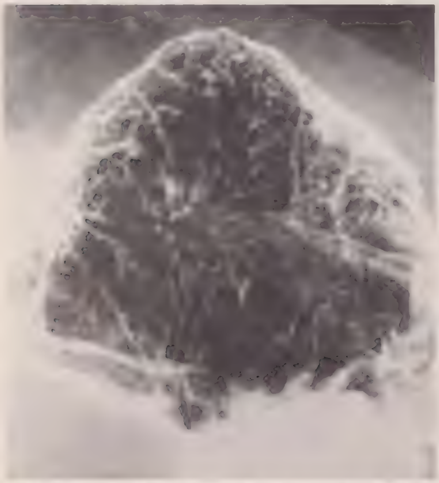


Fig. 11. Poor coating mimicks erosions in a patient with a double-contrast examination of a normal stomach.

relationship between the coarse pattern of the areae gastricae in the body and fundus and the gastric hypersecretory function. However, specific histologic diagnosis of gastritis was not made for any of the cases reported in that paper. In our experience the areae gastricae cannot be routinely visualized, which is contrary to the report of a success rate of up to 93% (29), nor can we confirm the report of excellent agreement (82%) between visualization of abnormal areae gastricae and the presence of gastritis (27).

Among the 68 patients with gastritis in our study, we obtained a mean sensitivity of 58% with the single-contrast examination of the upper gastrointestinal tract and of 72% with the double-contrast technique when all radiographs were analyzed, and these percentages rose to 59% for single-contrast radiography and 77% for the double-contrast radiography if only adequate examinations were included in the analysis. There was a statistically significant difference between the sensitivity of the two methods, but not between adequate examinations and all examinations within each method. The respective sensitivities of single-contrast and double-contrast examinations for mild gastritis were 53% and 70%, rising to 60% and 74% respectively for moderate to severe disease. The overall sensitivities for single-contrast (58%) and double-contrast (72%) radiography and the sensitivities for detecting erosive gastritis alone (55% for single-contrast and 68% for double-contrast examinations) are much higher than those reported by Ott et al (23), who found a sensitivity of 24% for single-contrast and 43% for double-contrast radiography in detecting erosive gastritis.

A direct comparison of the report by Ott et al (23) and our study is difficult because not all the signs we used were analyzed in their investigation. In our investigation, we had statistically



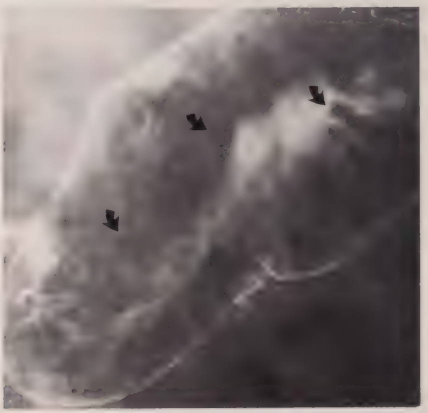


Fig. 12. Enlarged areae gastricae in the fundus are seen in a patient with nonerosive, nonspecific gastritis related to alcohol abuse.

Fig. 13. Diffusely irregular and enlarged areae gastricae (arrows) are a good sign of gastritis in this patient with a long history of peptic gastritis.

similar high numbers of false-positive findings for both techniques. One paper (30), while not specifying the radiographic technique used, did consider the radiographic examination useless for diagnosing gastritis, except that negative radiographic findings were deemed to be clinically important. Our results contradict this belief in that a false-negative finding of gastritis was rare with the double-contrast technique, particularly if a moderate or severe form of gastritis was present. If the diagnosis was based on one or two radiographic features, however, the false-positive findings were too high in either technique to make the technique reliable.

Our results might have been improved for both methods if glucagon had been used routinely. In an unpublished study, we found marked improvement of the sensitivity of double-contrast radiography for detecting superficial lesions in the upper gastrointestinal tract if 0.1 mg of glucagon was injected intravenously (31).

The sensitivity of each radiographic method sometimes is impaired by technical problems, including the presence of a large amount of secretion, blood clots, muscle spasms, or inadequate film exposure technique. During a review of the false-negative results in our study, we found that many subtle changes such as coarse areae gastricae or small erosions, particularly of the incomplete type, could be identified retrospectively. We also found that the use of magnification lenses to examine the radiographs improved sensitivity markedly. Nevertheless, many of the changes, such as submucosal hemorrhage, were too superficial to be detected radiographically, even with faultless technique. This fact contributed to the higher rate of false-negative findings associated with the mild forms of gastritis.

False positives invariably result from diagnoses of gastritis based on one or two features and usually are related to increased secretion and poor coating with barium. Occasionally, barium in the small bowel mimicks erosion by obscuring the antrum, the most common site of gastritis (20, 32).

Role of Endoscopy and Radiography

Our data suggest that double-contrast radiography is superior to single-contrast radiography for detecting gastritis, but both methods show slightly improved results when a moderate to severe form of gastritis is present. Both methods, however, have too high a number of false-positive findings and, therefore, cannot be used as the initial screening test. The endoscopic examination should remain the primary method of examining patients with suspected gastritis. Double-contrast radiography may be of use in patients who are not candidates for endoscopy or who have undergone an unsuccessful or incomplete endoscopic examination. In patients with proved gastritis, the double-contrast examination may be used as a follow-up to establish the success of treatment. Because most of the radiographic signs other than erosion do not assist in diagnosing a particular type of gastritis, we recommend that only the terms “erosive” or “nonerosive” be used for the radiographic diagnosis of nonspecific gastritis.

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The Esophagus and Stomach After Proximal Gastric Vagotomy

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Abstract

We reviewed surgical and medical records and pre- and post-operative upper gastrointestinal examinations on 17 patients who underwent proximal gastric vagotomy without drainage or antireflux procedures in order to describe the appearance of the postoperative esophagus and stomach. Narrowing of the gastroesophageal junction was present with or without associated dysphagia. The most common abnormality was an irregular, flattened, straightened or denuded lesser curvature, sometimes with an associated lesser-curvature mass. Infracardiac narrowing of the stomach was also a prominent feature, readily demonstrated on the right lateral view of the stomach and often also clearly apparent on frontal view.

Vagotomy for the treatment of peptic ulcer disease has undergone important changes in indications and technique since transthoracic vagotomy was introduced in the United States in 1943 by Dragstedt and Owens (1). Subsequent procedures—transabdominal (truncal) vagotomy, plus drainage or antrectomy, and selective vagotomy—were developed in response to continuing dissatisfaction with ulcer recurrence rates, diarrhea, dumping, gastric retention, and other complications that attend these procedures. Many of these complications are the result of loss, bypass, or mutilation of the antroplyoric pump. Therefore, any procedure that combines satisfactory reduction in acid production, acceptable rates of ulcer recurrence, preservation of antral innervation, and maintenance of gastroduodenal integrity is highly desirable (2). Proximal gastric vagotomy appears to satisfy these criteria (3, 4).

As with any operative procedure in the abdomen where anatomic relations are altered, problems in post-operative radiologic interpretation may arise. We report our experience with proximal gastric vagotomy to acquaint radiologists with the spectrum of changes that accompanies this operation.

Methods

Review of surgical records at the Dallas Veterans Administration Medical Center disclosed 28 patients in whom proximal gastric vagotomy alone (without gastric drainage procedures) had been performed from January 1977–December 1982, inclusive. Of these 28 patients, 19 had undergone both a pre- and post-operative upper-gastrointestinal (GI) examination. Because of poor-quality examinations that rendered assessment and comparison unsatisfactory, 2 of these patients were excluded from consideration. Thus, a total of 25 upper gastrointestinal examinations performed in the postoperative period on 17 patients constitutes the subject of this report. All patients had established peptic ulcer disease, complicated either by intractability or by upper-GI hemorrhage. No patient had clinical or radiographic evidence of reflux esophagitis prior to proximal gastric vagotomy. Patients underwent upper-GI barium studies in the postoperative period at intervals from two weeks to 42 months (mean, 7.4 months; median, 4.2 months). Indications for these postoperative examinations varied from asymptomatic follow-up (4 patients), to dysphagia (5 patients), to recurrent or continued abdominal pain (7 patients). Relevant clinical and operative information was extracted from the of-

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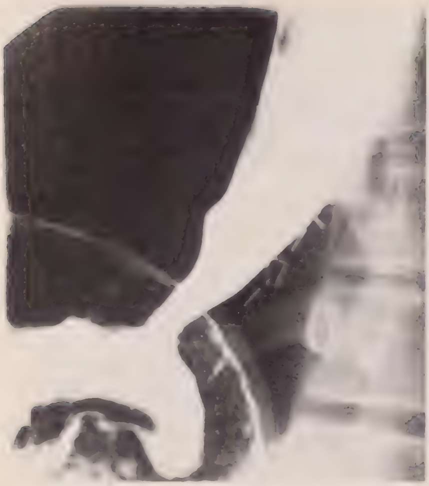

Fig. 1. Distal esophageal narrowing without fundoplication. Prone right anterior oblique view of region of gastroesophageal junction nine weeks after operation reveals narrowing of lower esophagus associated with proximal dilatation.

ficial surgical reports, reviews of medical and endoscopic records, and from the x-ray requisitions.

Results

Esophagus. The five radiographic abnormalities observed after surgery were distal esophageal narrowing; irregularity of the gastric cardia; infracardiac narrowing; lesser-curvature mass; straightened, flattened, irregular, or "denuded" lesser curvature.

Narrowing of the distal esophagus, associated with slight proximal dilatation, was present in five postoperative patients (Fig. 1). Of these five patients, who demonstrated structural abnormality of the lower esophagus at intervals ranging from three weeks to 6.75 months (mean, 3.75 months), only two had dysphagia. Another five patients had upper-GI examinations performed because of complaints of dysphagia. Two of these had normal esophagograms; one had a small (probably insignificant) "B" ring, unchanged from the preoperative appearance; two revealed lower esophageal narrowing not present on preoperative examinations.

Stomach. The most striking and frequent abnormalities were related to the stomach. The lesser curvature of the stomach was regularly straightened, flattened, or appeared "denuded" or irregular from the infracardiac region to within several centimeters of the incisura angularis (Fig. 2). These deformities of the lesser curvature were at times associated with a soft-tissue mass of variable length and prominence. The appearance varied from a subtle change noticeable on a single view to a prominent deformity evident on many views (Fig. 3).

Infracardiac narrowing, sometimes simulating the "hourglass" deformity due to ulcer disease on the lesser curvature (Fig. 4), was also frequently present. The gastric-body narrowing was most easily appreciated on the right lateral view; it could be noted, however, on frontal views as well (Fig. 4).

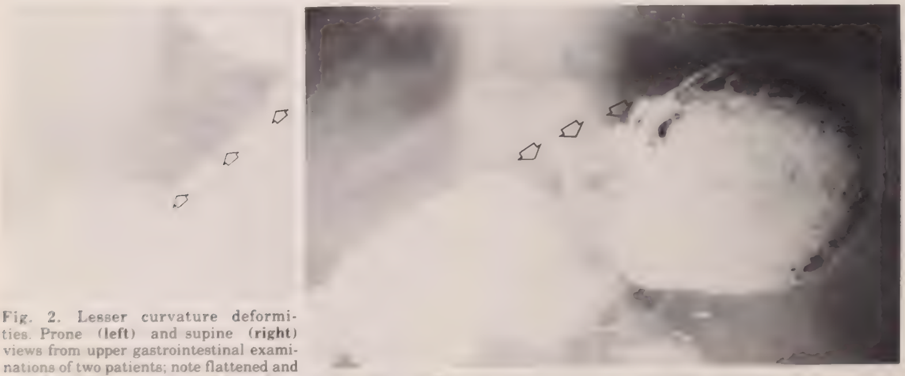

Fig. 2. Lesser curvature deformities. Prone **(left)** and supine **(right)** views from upper gastrointestinal examinations of two patients; note flattened and straightened appearance (left) and irregular and "denuded" proximal lesser curvature **(right)** (arrows).

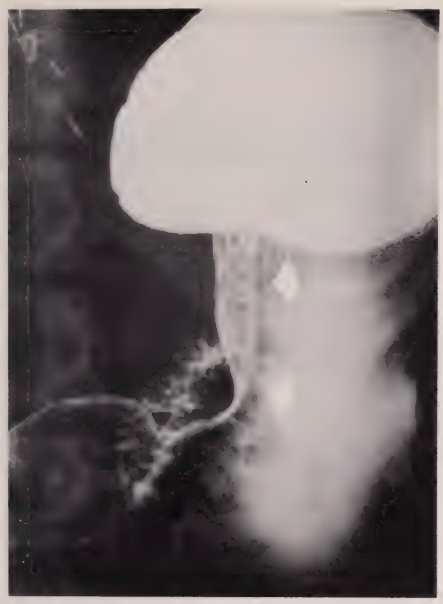

Fig. 3. Lesser curvature mass. Supine view of stomach shows prominent lesser curvature mass extending from cardia to incisura angularis (arrows).

Discussion

The proximal gastric vagotomy—also called parietal cell, superselective, selective-proximal, proximal-selective, and highly selective vagotomy—denervates only that portion of the stomach that bears parietal cells. Because vagal contributions to the cardia may be derived from branches in and around the distal esophagus, it is imperative that dissection be carried 5–7 cm up along the distal segment of the esophagus. To insure complete denervation of this region, some surgeons routinely perform esophageal "scoring," that is, circumcision of the superficial muscle layers of the lower esophagus. The gastric branches are then bluntly dissected free and all the branches to the cardia and body are sectioned, sparing in each case the nerve of Latarjet that innervates the distal stomach. Antral and pyloric innervation is thereby preserved. This operation differs from earlier procedures, such as truncal vagotomies, in which all branches and plexuses at the level of the esophagus were sectioned.

Although proximal gastric vagotomy has enjoyed recent, but short-term, success as a treatment of peptic ulcer disease, the procedure is not without problems. Postoperative dysphagia has been prominent. Three of 41 patients interviewed at two months by Jordan (5) had dysphagia. Amdrup et al reported an incidence of 12% dysphagia when proximal gastric vagotomy alone was performed and of 6% when it was accompanied by gastric drainage procedures (4). Relationship of this dysphagia to the extensive mobilization and skeletonization of the lower esophagus, to postoperative periesophageal edema or hematoma, or to the maneuver of esophageal scoring is wholly speculative. It is clear, however, from our series and others (4–6) that postoperative dysphagia occurs in the absence of concurrent antireflux procedures, for example Nissen fundoplication, and in the absence of esophageal scoring. Most such occurrences of dysphagia are transitory, typically remitting by three to six months (4, 5).

The irregular, denuded appearance of the lesser curvature results from the denervation (and partial devascularization) of the region in order to reduce parietal cell function. The lesser curvature "mass" is the result of invagination of this region through a technique described as imbrication. The size and extent of this lesser curvature mass—it may extend proximally to the gastroesophageal junction—will depend on (a) the degree of invagination, (b) the depth of the surgeon's "bite" taken to close the lesser curvature, and (c) the proximal extent of this procedure (Fig. 5). This maneuver—imbrication—is designed to reserosalize the now partially devascularized lesser curvature so as to lessen the morbidity and mortality associated with free intraperitoneal rupture of the stomach that may result from ischemic necrosis of the lesser curvature after prox-

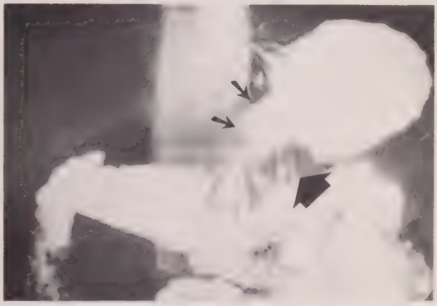

Fig. 4. Infracardiac narrowing. Supine image of stomach reveals markedly narrowed midbody (large arrows) with resultant "hourglass" deformity and lesser curvature pseudo-ulcer (small arrows).

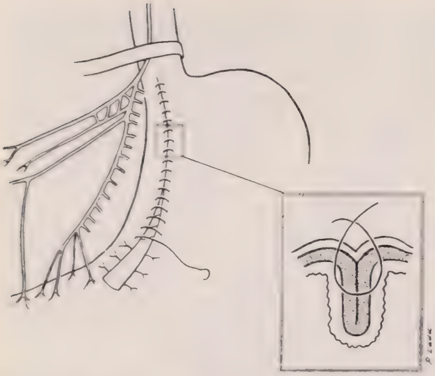

Fig. 5. Technique of imbrication. Lesser curvature of stomach at completion of proximal gastric vagotomy. Note specific sectioning of gastric parietal branches, antral and other visceral branches being preserved. Reperitonealization and invagination—imbrication—of lesser curvature is depicted in inset.

imal gastric vagotomy (7). The explanation for the gastric narrowing is not as clear; this narrowing, too, may relate to the type of lesser curvature imbrication. Although imbrication was routinely performed in our patients, the narrowing of the body of the stomach was not a universal phenomenon.

Acknowledgments

The authors acknowledge the assistance of members of the general surgery and gastroenterology staffs at the Dallas Veterans Administration Medical Center in the preparation of this report.

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Abnormal Mucosal Fold Patterns in the Duodenum

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The responses of the duodenum to disease, like those of the rest of the gastrointestinal tract, are limited. One of these responses consists of changes in the thickness, number, and pattern of the mucosal folds. In many instances, these changes are nonspecific, but in some there are clues, both radiologic and clinical, which point toward a specific diagnosis. An awareness of these clues and patterns is important for the proper radiologic evaluation of these abnormal patterns.

Duodenitis. The commonest cause of thickening of the duodenal mucosal folds is peptic ulcer disease. Apparently, the increased acid production causes mucosal edema, although hyperplasia of Brunner's gland may also play a role. The transition between the normal and abnormal fold patterns is usually located at the mid descending duodenum, due to the entrance at this point of the alkaline bile and pancreatic secretions, which effectively neutralize the acid gastic secretions (Fig. 1). Occasionally, when acid production is excessive, as in some patients with Zollinger-Ellison syndrome, the fold thickening may extend to or beyond the ligament of Treitz (Fig. 2).

An exogenous source of acid, such as acid drunk by accident or in a suicide attempt, can produce a similar picture except that gastric and frequently esophageal damage (1) are usually present.

A similar thickening of the mucosal folds also occurs in patients with acute pancreatitis. The distribution may be diffuse, involving the entire duodenal loop, or segmental (Figs. 3, 4).

At times the medial border of the second duodenum is flattened due to the pressure of an enlarged pancreatic head, and this constitutes a valuable clue to the diagnosis.

Cystic Fibrosis. According to Taussig et al (2), duodenal abnormalities occurred in 84% of 33 cystic fibrosis patients, whose age ranged from 4 to 42 years. These abnormalities consisted of a thickened, coarse fold pattern, nodular indentations along the duodenal wall, smudging of the fold pattern, and distortion and kinking of the duodenal contour. These changes were usually confined to the first and second portions of the duodenum (Fig. 5).

Taussig et al could find no correlation between the gross and microscopic findings and the radiologic appearances. Clemett (3) speculated that the pattern might be attributed to an increased number of goblet cells, dilatation of mucous glands, and mucus adherent to the mucosal surface. Pancreatic insufficiency per se does not seem to be the cause since 21 patients studied by Taussig et al with documented lack of pancreatic enzymes did not have mucosal abnormalities. These authors also stated that "the repeated demonstrations of indentations along the lateral duodenal wall in the same patient over a period of months and years and the absence of demonstrable irregularities of the inner wall on hypotonic duodenography virtually exclude adherent mucus as the cause of the abnormalities."

Changes in the mesenteric small bowel are infrequent in this condition.

Celiac Sprue. Nicoletti and Tully, in 1971 (4), first called attention to the striking changes in the duodenum in patients with celiac sprue, in contrast to the minimal changes usually present in the mesenteric small intestine (Fig. 6). Thickening of the folds together with a decrease in their number and an asymmetric distribution were noted in 25 of 30 cases. These changes are largely limited to the first and second portions of

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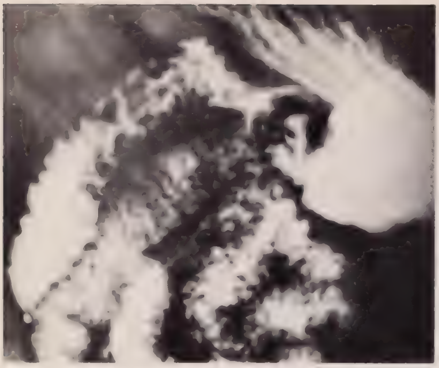


Fig. 1. Thickened, nodular mucosal folds involving bulb and proximal half of descending duodenum, characteristic of duodenitis. Neutralization of acid by alkaline pancreatic juices explains resumption of normal folds at mid descending duodenum.

the duodenum, with a gradual transition to a normal fold pattern in the distal duodenum. In the mesenteric small bowel, the changes associated with celiac sprue consist only of mild dilatation, while the mucosal folds usually remain normal.

The cause of the striking mucosal duodenal alterations is unknown, and correlations between microscopic changes seen on biopsy specimens and roentgenographic findings have not been found.

Crohn's Disease. Involvement of the duodenum by Crohn's disease is uncommon although not by any means rare. According to Nugent et al (5), it represents 2% of the cases of Crohn's disease at the Lahey Clinic. In most patients, there is evidence of the disease elsewhere in the gut. Occasionally, the disease develops first in the duodenum; in rare cases disease is confined to the duodenum. In the latter instance, there is usually histologic evidence of antral disease, even though the antrum may seem normal radiologically.

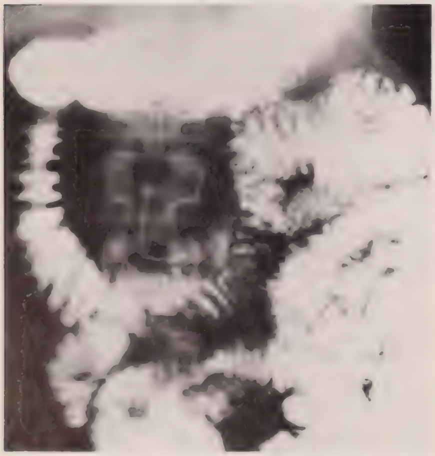


Fig. 2. Thickened folds in entire duodenal loop and in proximal jejunum, in patient with proven Zollinger-Ellison syndrome.

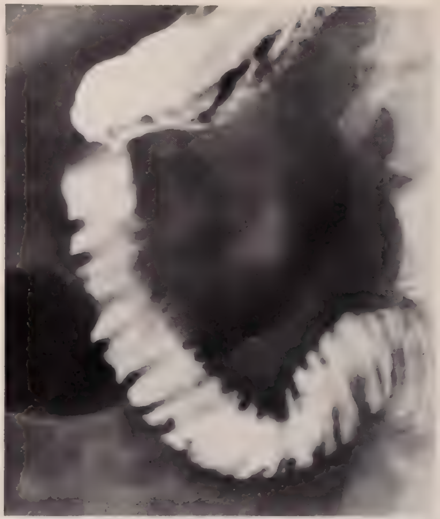


Fig. 3. Uniform thickening of duodenal folds associated with acute pancreatitis. Flattening of medial contour suggests enlargement of pancreatic head.

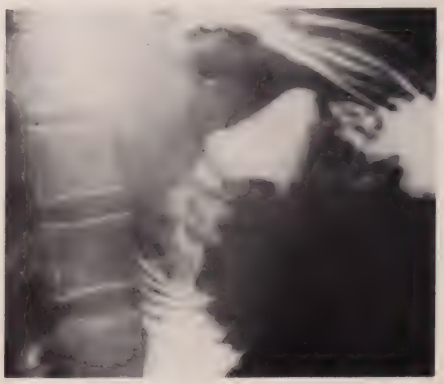


Fig. 4. Segmental involvement of proximal descending duodenum, in patient with acute pancreatitis.

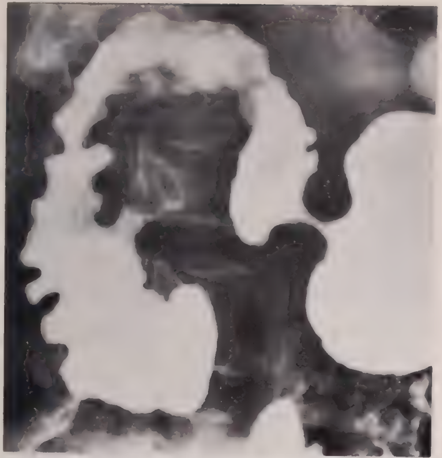


Fig. 5. Abnormal contour with coarse folds involving entire duodenum, in 30-year-old man with cystic fibrosis. Mesenteric small bowel was also dilated, with thickened mucosal folds.

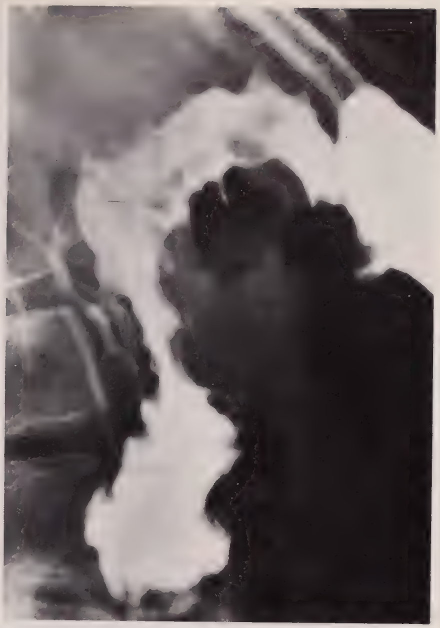


Fig. 7. Crohn's disease of duodenum in 14-year-old boy with midepigastric pain and protein loss. Terminal ileum and cecum were also involved.

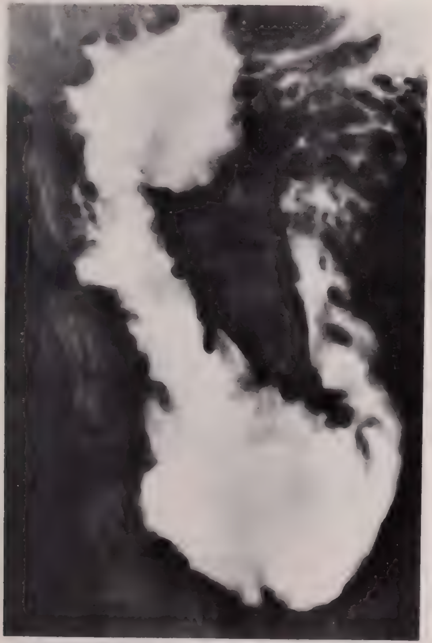


Fig. 6. Coarse, irregular folds involving entire duodenum in 57-year-old woman with nontropical sprue (gluten-enteropathy). Mesenteric small bowel was normal. Complete clinical remission after 3 weeks on gluten-free diet.

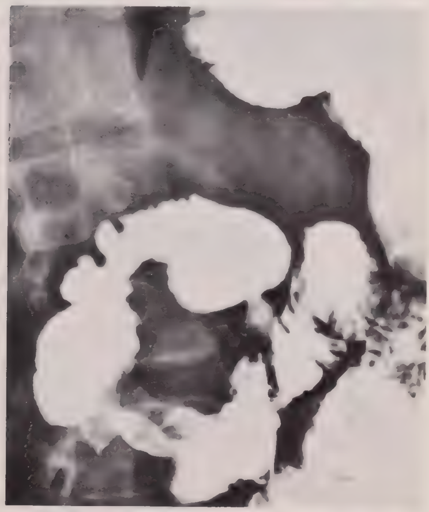


Fig. 8. Crohn's disease limited to second duodenum. Note thick folds, normal duodenal bulb, and focal ulceration at junction of second and third duodenum.

Three patterns may be observed radiologically, the most common being simultaneous involvement of the gastric antrum and the adjacent proximal duodenum. In the second pattern, the disease is limited to the second duodenum (Figs. 7, 8). The third and least common pattern is disease of the third duodenum, usually with contiguous involvement of the proximal jejunum (Fig. 9).

The radiologic features are similar to those found in other parts of the gut: irregular, thickened folds, ulcerations, and stenoses. In the first pattern, the anatomic landmarks between the base of the bulb, the pylorus, and antrum are obliterated, producing the "pseudo-Billroth I" appearance, or "ram's-horn" sign (6, 7) (Fig. 10).

Reflux of barium into the pancreatic and common bile ducts may be observed (8). This is not specific, since this phenomenon has also been seen in a variety of other infiltrative conditions including strongyloides and lymphoma.

Intramural Hematoma. Trauma is the commonest cause of intramural hematoma of the duodenum, but it may also occur spontaneously in patients receiving anticoagulant therapy, or associated with acute pancreatitis, ruptured aneurysm, or hemorrhagic diatheses of various etiologies (9, 10), including hemophilia; 60% of intramural hematomas are said to occur in children.

The roentgen appearance of the hematoma is the same regardless of the cause of the underlying edema and hemorrhage, and it is quite characteristic. The lumen is narrowed, with associated diminished distensibility. Peristaltic activity is usually absent or diminished, so that stasis in the affected segment is frequent. The most dramatic finding is the replacement of the mucosal folds by stretched swollen folds to produce a sharp, spikelike contour which has been likened to a "picket fence" or "stack of coins" (Fig. 11). At times, a second pattern is produced in which the valvulae conniventes are completely effaced, probably due to a more severe submucosal hemorrhage. A changing configuration from effacement to a serrated appearance has been observed during healing (11).

The duodenum seems to be unusually predisposed to trauma, presumably because of its fixation in the retroperitoneal area, in contrast to the mobile mesenteric small bowel. Intramural hematomas are self limiting and complete spontaneous reversion to normal practically always occurs.

Cryptosporidiosis. *Cryptosporidium,* a parasitic protozoan found in the gastrointestinal tracts of a variety of animals, has recently been reported in immunologically incompetent patients, including patients with AIDS syndrome. More recently, five cases have been reported in immunocompetent persons (12). In immune-competent patients, the disease is a moderate, self-limited one, but it is prolonged and severe in immunocompromised patients.

The radiologic manifestations may be limited to the duodenum and consist of irregularly thickened mucosal folds, especially in the second duodenum, and are radiographically indistinguishable from Crohn's disease, sprue, and mucoviscidosis (Fig. 12). With special techniques the oocysts can be identified in fecal flotations.

Cutaneous Diseases. Schönlein-Henoch purpura belongs to the group of leukocytoclastic angiitis disorders. The basic pathology is an acute necrotizing process that involves venules and postcapillary venules in the skin, gut, and other internal organs. Thus, in the duodenum it produces the picture of an intramural hemorrhage (Fig. 13). This may be isolated or associated with similar findings in other parts of the intestinal tract.

Chronic urticaria frequently involves the gut, and at times may be limited to the duodenum. Although there are many known causes for this condition, in most instances it is idiopathic (13). The skin lesions are characteristic, and one must only remember that internal organs may be similarly involved (Fig. 14).

Cronkhite-Canada Syndrome. Diffuse polypoid changes in the duodenal loop may be found in Cronkhite-Canada syndrome. These changes are not limited to the duodenum (Fig. 15) but are always associated with similar mucosal hypertrophy or a polypoid appearance in the stomach, small bowel, and colon (14). This, plus the other clinical features of diffuse brownish pigmentation of the skin, onychotropia, and alopecia, facilitates recognition of this syndrome. The intestinal polyps, originally deemed adenomatous, are now accepted to be inflammatory pseudopolyps rather than neoplasms, and are composed of cystically dilated hyperplastic glands filled with mucus, with marked stromal edema. The clinical manifestations include severe, watery diarrhea, malabsorption, tetany, steatorrhea, and marked protein loss due to exudative enteropathy.

The prognosis is poor, especially in women, whereas in men there is a tendency for remission. The differential diagnosis must take into account Peutz-Jeghers syndrome and Gardner's syndrome.

Klippel-Trenaunay Syndrome. The appearance of phleboliths anywhere in the body, with the exception of the pelvic region, usually signifies the

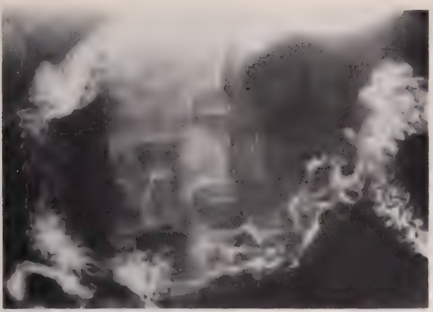


Fig. 9. Type III pattern of duodenal Crohn's disease limited to third duodenum and ending at ligament of Treitz.

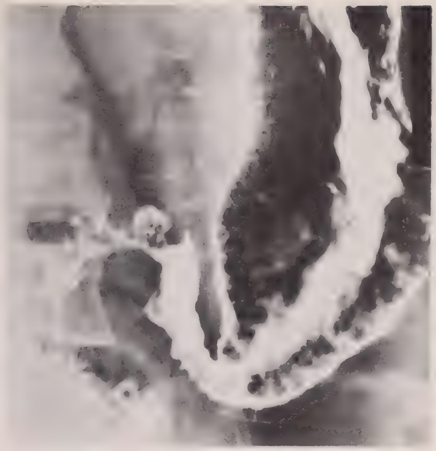
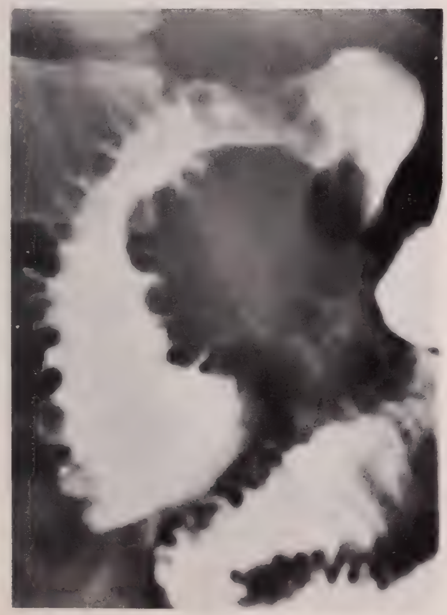


Fig. 10. Crohn's disease involving distal stomach and duodenal bulb, producing "pseudo-Billroth I" appearance.

presence of a hemangioma. The phleboliths in the right upper quadrant demonstrated in Fig. 16 and associated with prominent, irregular, tortuous duodenal mucosal folds suggest that the hemangioma is located within the duodenal walls. This patient also had bony and soft tissue overgrowth of the right upper extremity; this constellation of findings is compatible with the Klippel-Trenaunay syndrome (15–17). This association of soft tissue and bony hypertrophy, cutaneous hemangioma of the "port-wine" variety, and varicose veins was first described by Klippel and Trenaunay in 1900. Parkes Weber described a similar entity with the addition of an arteriovenous fistula. The occurrence of a visceral hemangiomatosis in this entity is rare and most commonly



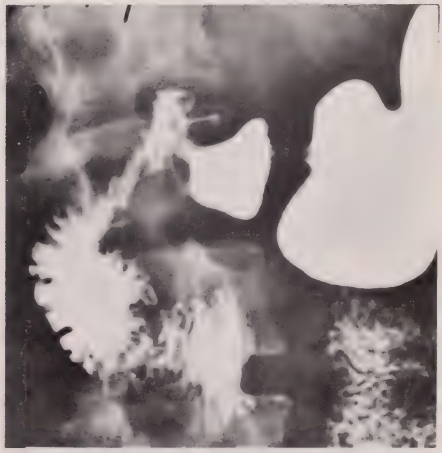


Fig. 11. **Left** Thickened folds with smooth, spiculated contour characteristic of submucosal edema or hemorrhage, in motorcyclist struck by car. **Right** Reversion to normal, one week later.

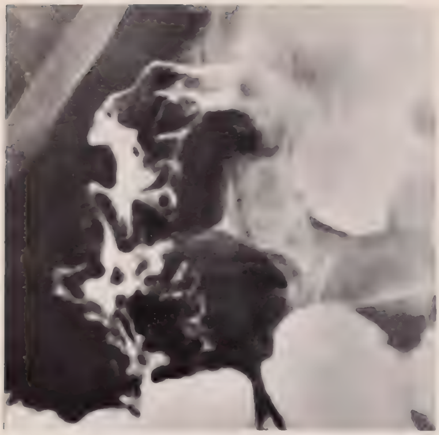


Fig. 12. Cryptosporidiosis in patient with AIDS. Nonspecific, irregular fold enlargement.

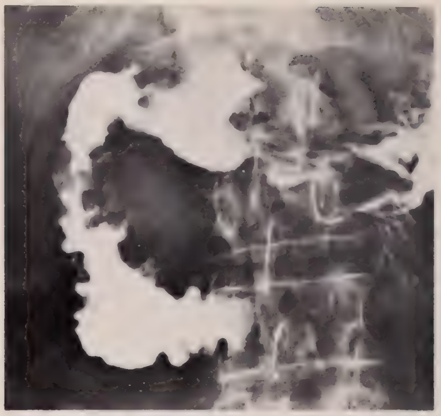


Fig. 14. Thickened irregular folds involving entire duodenum in 56-year-old woman with severe urticaria; mesenteric small bowel was normal.

involves the rectum, with associated rectal bleeding. Usually only one of the lower extremities is involved and the hemangioma is located in the duodenum.

Strongyloidiasis. *Strongyloides stercoralis* is a nematode that has a worldwide distribution but is more prevalent in warm tropical areas. The free adult form lives in warm, moist soil, but under certain conditions it can metamorphose into an infective, filariform type which penetrates skin or mucosa and spreads via the blood stream. In the gastrointestinal tract, the males are excreted but the females burrow into the intestinal mucosa, chiefly in the duodenum and proximal jejunum, although any part of the small or large bowel may be invaded. These adult females produce filariform larvae which gain access to the blood stream through the intestinal mucosa or perianal skin, so that autoinfection occurs. This perpetuates the life cycle of this parasite even after the patient leaves the endemic region. Humans may carry parasites for years without

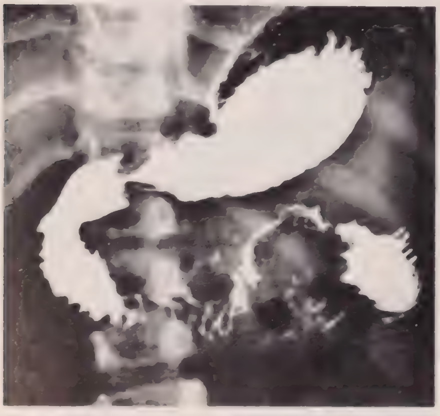


Fig. 13. Coarse folds in patient with Schönlein-Henoch purpura. Smooth contour and sharp points are characteristic of submucosal hemorrhage and edema. Association of polyarthralgia, cutaneous purpura, and guaiac positive stools helped establish diagnosis.

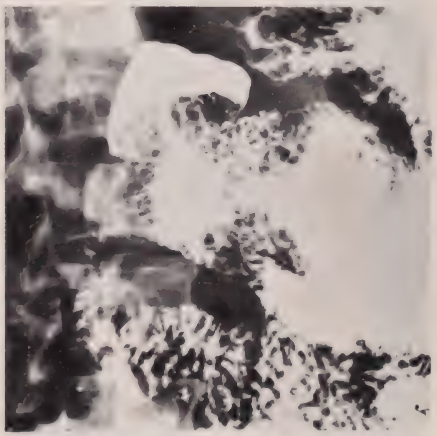


Fig. 15. Coarse, nodular fold involving duodenum and distal stomach in 61-year-old man with Cronkhite-Canada syndrome. Diarrhea, weight loss, alopecia, and onychodystrophy completed the clinical syndrome.

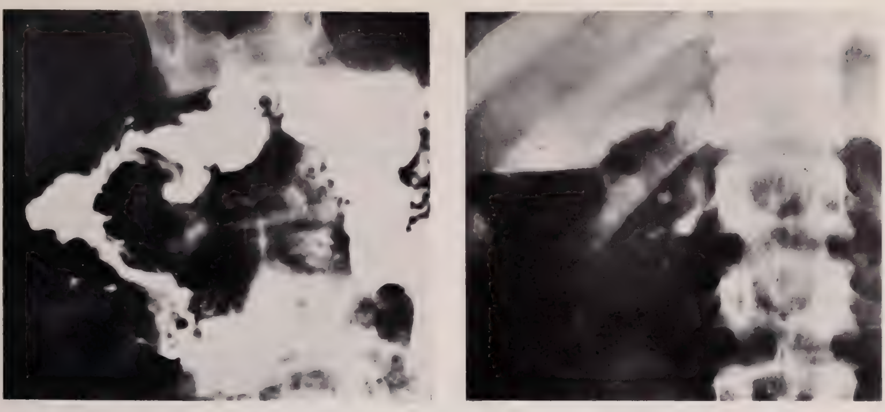


Fig. 16. **Left** Coarse nodular folds in patient with Klippel-Trenaunay syndrome. **Right** Intramural calcification characteristic of phlebolith visible on plain film.

symptoms. However, this benign postparasite relationship may be impaired by chronic infection, malnutrition, cancer, or impairment of the body's immune defenses (18–20).

The classical radiological appearance is that of effacement of the mucosal folds of the entire duodenal loop due to lymphatic obstruction and granulomatous reaction. Multiple strictures and linear mucosal ulcers are frequent (Fig. 17). In milder cases, only swollen mucosal folds may be present. Involvement of the proximal jejunum is common.

The differential diagnosis includes consideration of Crohn's disease, but strongyloidiasis rarely involves the terminal ileum. Primary lymphoma of the small bowel could also simulate this radiographic appearance, but the length of the segment of the involved bowel would be very unusual in lymphoma.

Stool specimens will usually not contain eggs, and the diagnosis is best established by biopsy or duodenal fluid aspiration.

Clinical manifestations include vomiting, diarrhea, and weight loss. Epigastric pain may mimic peptic ulcer disease. Occult bleeding is common, secondary to mucosal ulcerations or disseminated

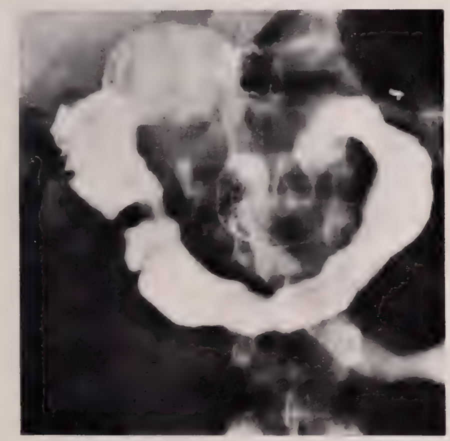


Fig. 17. Effacement of folds involving entire duodenal circle and proximal jejunum, in patient with *Strongyloides* infection. Note reflux into common bile and pancreatic duct (arrows) and a few constant areas of stenosis in mid descending duodenum.

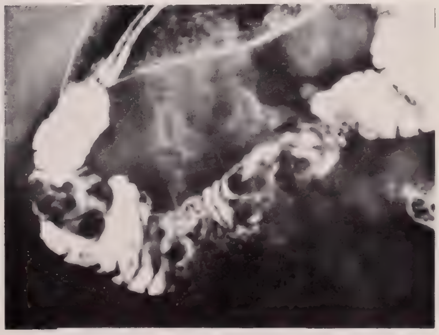


Fig. 18. Duodenal varices in patient with alcoholic cirrhosis and calcific pancreatitis. Focal nature of thickened folds and pancreatic calcification near ligament of Treitz provide valuable clues to diagnosis.

intravascular coagulopathy. Enteropathy causing protein loss and malabsorption mimicking sprue has been reported.

Duodenal Varices. Duodenal varices may result from both intrahepatic and extrahepatic portal obstructions. Duodenal varices unassociated with esophageal varices are rare—Itzchak and Glickman (21), in 1975, could only find 35 reported cases. Duodenal bulb deformities were most commonly seen, and it is difficult to distinguish these varices from peptic ulcer disease, which commonly coexists with cirrhosis. However, Itzchak and Glickman noted, in 10 patients, sharply marginated folds along the contour of the proximal second duodenum—a location and appearance which seem to be characteristic. Focal nodular lesions in the mid descending duodenum have also been described (Fig. 18).

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Carcinoma of the Esophagus: Its Varied Radiologic Features

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Abstract

Carcinoma of the esophagus is the most common tumor of the esophagus and constitutes 4% of all malignant tumors of the gastrointestinal tract. A retrospective review and analysis of 390 patients afflicted with carcinoma of the esophagus seen at the University of Michigan, Ann Arbor, revealed a variegated spectrum of radiologic features. Diagnosis of typical advanced carcinoma is relatively straightforward; however, it is easy to miss the subtle changes in the esophagus due to early carcinoma, which may present as a small plaque-like elevated lesion, a small sessile polypoid lesion, or a localized area of rigidity of the esophageal wall. The diagnosis requires a high index of suspicion and careful attention during fluoroscopic and radiographic examination. In this study, unusual roentgen features consisted of varicoid carcinoma simulating esophageal varices, primary ulcerative carcinoma showing Kirklin Carman meniscus complex, smooth strictures simulating benign peptic strictures, diffuse involvement of the entire esophagus by carcinoma and multiple (multicentric) carcinomas of the esophagus. Carcinoma complicating columnar-lined (Barrett) esophagus and long standing achalasia pose particular diagnostic problems to the radiologist. The usual and unusual roentgen features of carcinoma of the esophagus and many practical diagnostic challenges are discussed and illustrated.

In 1983, there were approximately 9,000 new cases of carcinoma of the esophagus and 8,500 deaths (1). Unfortunately, the relative five-year survival of 4% has remained unchanged from the figure obtained in the early 1960s by the National Cancer Institute. Advances in surgical techniques, postoperative care, and radiation therapy have led to improved palliation, but have had little impact on cure rates when compared to the previous decade. This dismal outlook is mostly due to the late onset of dysphagia, which usually is the symptom that prompts these patients to seek medical advice. By the time dysphagia sets in, the esophageal lumen is reduced to one half to one third of its original diameter, and there is local as well as regional metastatic spread. If survival is to be improved in this disease, diagnosis of early carcinoma is imperative.

In this retrospective review of 390 cases of carcinoma of the esophagus seen at our institution over 26 years (1956–1982), a wide spectrum of distinct radiologic features were recognized. The usual and unusual roentgen presentations as well as certain diagnostic challenges in relation to this carcinoma constitute the basis of this paper.

Materials and Methods

Data was collected from the tumor registry at the University of Michigan, Ann Arbor. A total of 397 patients were registered under carcinoma of the esophagus for the period between January 1956 through December 1982. Seven patients were excluded from this study because the final histopathologic diagnosis was leiomyosarcoma, in two, and metastatic carcinoma to the esophagus, in five. Thus, 390 patients with primary carcinoma of the esophagus were the subjects for this study. There were 290 men and 100 women, ranging in age from 23 to 92 years, with an average age at diagnosis of 66 years; 85% of the patients were between the ages of 50 and 80 years

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(Table 1). There were 90 white, and 300 black, patients.

The histologic cell types among these 390 patients are summarized in Table 2. About 20.5% of the carcinomas were located in the upper third of the esophagus, 43.5% in the middle third, and 36% in the lower third.

Complete clinical data, modes of therapy, and survival data were available. Radiographic studies of 200 patients were available for review.

Results

Seventy-five percent of the patients had typical roentgen features of advanced carcinoma, consisting predominantly of the polypoid fungating and annular constricting types. Ten percent of the patients presented with primary ulcerative-type lesion. Mixed patterns were frequent in many advanced lesions.

Five patients presented with a varicoid pattern and three with smooth elongated tapering strictures simulating benign peptic strictures. Diffuse carcinoma involving the entire esophagus was seen in one patient and multiple carcinomas of the esophagus were seen in three patients. There were two patients with achalasia, and twenty-three patients with Barrett esophagus complicated by carcinoma.

Discussion

A variety of radiologic appearances of carcinoma of the esophagus are known (2–7). The usual and typical features of an advanced carcinoma pose no diagnostic problems. However, the roentgen features of an early carcinoma can be quite subtle. Several unusual presentations plague radiologists from time to time, and merit particular attention. We discuss usual and unusual roentgen features, radiologic diagnosis of an early esophageal carcinoma, and several challenging diagnostic problems that have emerged from this study.

TABLE 1
Age and Site Distribution of 390 Cases of Primary Carcinoma of Esophagus

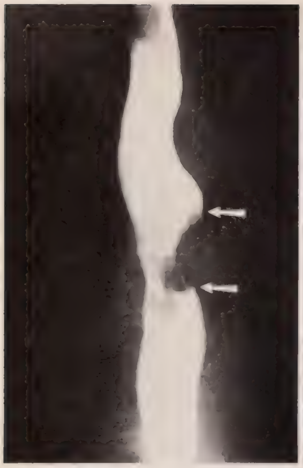
	Number	Percentage
Age range, yrs*		
0–30	1 (23 yrs)	0.25%
30–40	6	1.5%
40–50	37	9.4%
50–60	103	26.4%
60–70	155	39.7%
70–80	72	18.5%
80–90	15	3.8%
90–100	1 (92 yrs)	0.25%
Site		
Upper third	80	20.51%
Middle third	170	43.58%
Lower third	140	35.89%

* 85% of cases aged 50–80 yrs.

TABLE 2
Histologic Cell Types in 390 Cases of Primary Carcinoma of Esophagus

Cell Type	No. (%)
Squamous-cell carcinoma	
well differentiated	152
moderately differentiated	108
poorly differentiated	60
Total	320 (82.0%)
Adenocarcinoma	
well differentiated	14
moderately differentiated	12
poorly differentiated	15
mucin producing	1
Total	42 (10.76%)
Undifferentiated	24 6.15%
Carcinoma in-situ	2 0.51%
Mixed cell tumor (adeno and squamous)	2 0.51%

Usual Roentgen Features. There are three basic patterns to the gross appearance of esophageal carcinoma: polypoid, infiltrating, and ulcerating. On contrast studies, most advanced carcinomas appear as a bulky polypoid endophytic lesion (Fig. 1) or an annular constricting "apple-core" tumor, with over-hanging margins. Some ulceration is usually present, but primary ulcerative lesions are uncommon. Combinations of these three basic patterns are frequently seen (Figs. 2, 3). Perforating carcinoma with mediastinal abscess (Fig. 4) or tracheoesophageal fistula may be the first presentation. Despite extensive disease at the time of presentation, 8%–10% of the carcinomas are missed on the initial examination, while another 15% are diagnosed as something other than carcinoma (8, 9). Moderate sized lesions, 1.5–3 cm in diameter, generally occur as polypoid sessile lesions that are eccentric, may show ulceration, and irregularly narrow the lumen. Evaluation for advanced esophageal carcinoma is generally readily accomplished by single contrast examination. Size, location, and morphologic characteristics of a lesion sufficiently large to cause dysphagia can be demonstrated on views of the barium-filled esophagus. Adequate distention is essential to define the margins of the lesion. Mucosal relief views of the esophagus are often useful for evaluating fold pattern and surface characteristics of the lesions.



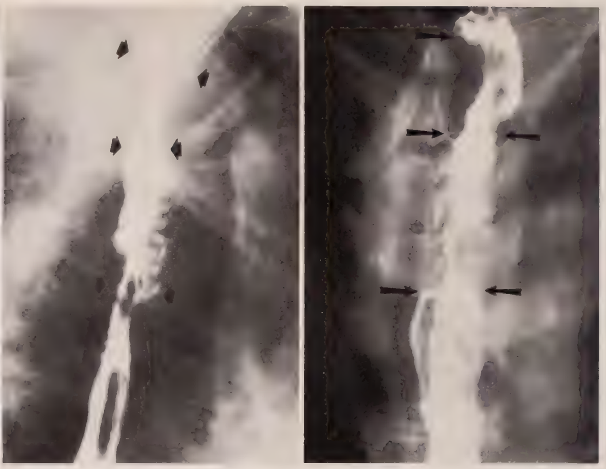


Fig. 1. Left Polypoid carcinoma. Posteroanterior view of barium-filled esophagus showing sharply delineated, rather smoothly rounded mass 3.5 cm in diameter, occupying almost entire lumen of esophagus. It arises from left and posterior wall. Mucosal origin is evident from acute angles at upper and lower margins of its posterior attachment (arrows).

Fig. 2. Center Infiltrative and ulcerative carcinoma. Right anterior oblique view from esophagogram, showing extensive neoplastic involvement of upper half of thoracic esophagus. Upper 3-cm segment of lesion shows typical annular, constricting or apple-core configuration, lower 5-cm segment shows extensive mucosal destruction and mucosal nodularity. **Right** Posterior anterior view of same lesion showing abrupt transition between normal and abnormal mucosa delineating the lower margin of the tumor (lower arrows).

Early Carcinoma. Roentgen features of an early esophageal carcinoma can be subtle and easily overlooked. From a review of our own case material and of recent reports by others (10–12), a rather characteristic radiologic appearance emerges. An early esophageal carcinoma tends to appear as a plaque (Fig. 5) or flat sessile polyp extending less than 1 cm into the esophageal lumen (Fig. 6). Ulceration may be present. The ulcer tends to be single and central. These plaque-like flat lesions are difficult to demonstrate. Our experience, as well as recent reports, suggests that the double-contrast esophagogram using a high-density barium mixture in a thin coating on a distended esophagus is the best method currently available for identifying small esophageal tumors. With single-contrast views, a high-kilovoltage technique should be used to visualize the mucosal detail. With either technique, the esophagus should be examined in at least four projections to evaluate the entire circumference, because many small tumors alter the contour of only one wall.

Other important signs of early carcinoma of the esophagus are areas of subtle wall rigidity, lack of distensibility or a small segment in which there is decreased compliance (Fig. 7). Double-contrast views have been found to be excellent for detecting small areas of subtle inelasticity in the esophageal wall.

Esophageal peristalsis is intact in the majority of patients with small esophageal carcinomas. Careful observation of the esophageal stripping wave as it traverses the esophagus is helpful in detecting small carcinomas. In a barium-filled esophagus, small hidden tumors are frequently observed during the passage of the tail of the barium bolus. These lesions often "pop" into view when squeezed by the aborally directed wave of circular peristaltic contractions (7) (Fig. 8). Thus, careful attention to several peristaltic sequences during routine upper-gastrointestinal examination offers some opportunity for detecting small nodular or plaque-like lesions that are not observable on conventional films. In an asymptomatic patient, a flat sessile polyp presenting as a small area of thickened mucosal fold overlaid with granular mucosa, with or without central ulceration, can be a difficult diagnostic challenge. Endoscopy and biopsy is usually necessary for diagnosis.

Primary Ulcerative Carcinoma. Polypoid fungating or annular constricting types of carcinomas comprise the majority (75%) of lesions, and

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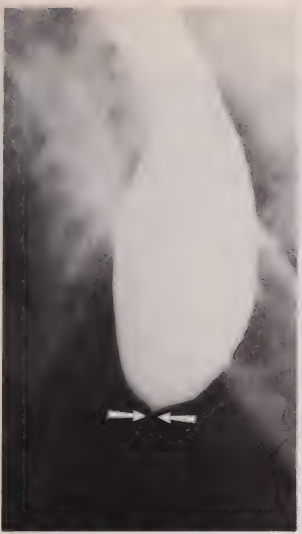
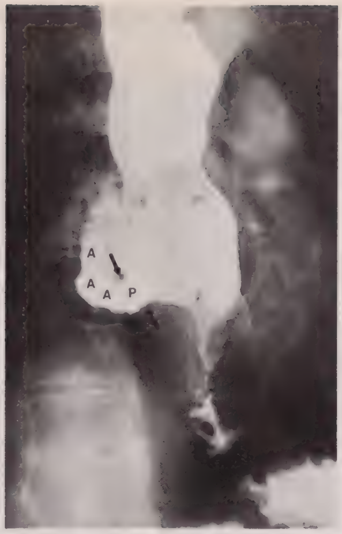




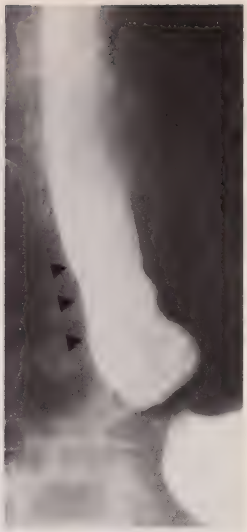


Fig. 3. Left Obstructing infiltrative carcinoma. Lateral view of barium-filled thoracic esophagus. Complete obstruction of esophagus with short and sharp terminus (arrows) and dilated proximal esophagus. Slightly asymmetrical character and minimal nodularity along posterior wall at and above level of obstruction are characteristic of malignancy.

Fig. 4. Center Perforating carcinoma with mediastinal abscess. Posteroanterior view of barium-filled esophagus, showing extensive infiltrative (stenosing) lesion involving lower third of esophagus with dilated proximal esophagus. Tumor has perforated (P) through right wall of the esophagus; barium is tracking into mediastinal abscess (A).

Fig. 5. Right Plaquelike carcinoma (arrowheads), 1.3 cm in length (smallest tumor in our series), involving one wall of esophagus. Endoscopy confirmed this lesion and biopsy revealed squamous-cell carcinoma.

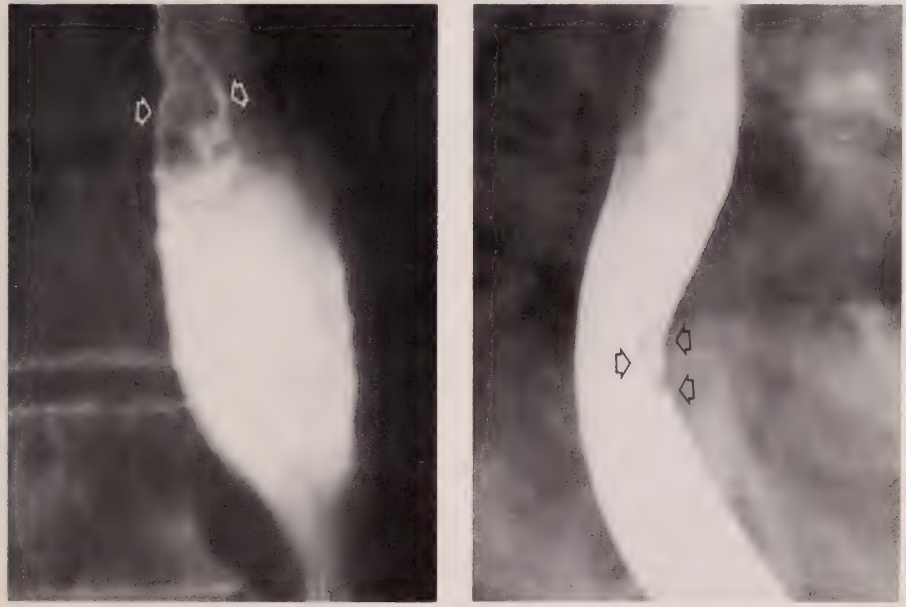


Fig. 6. Left Double-contrast view of esophagus shows 2-cm sessile polypoid carcinoma (open white arrows) with small central ulcer. **Right** Single-contrast view of same esophagus in right anterior oblique projection, showing small polypoid mass with central ulceration (open black arrows).

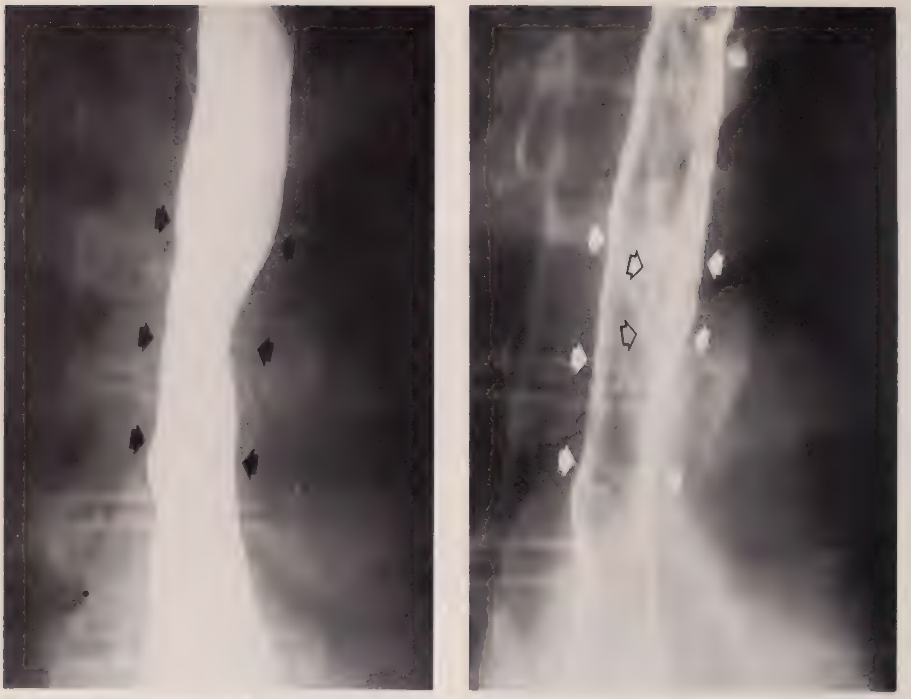


Fig. 7. **Left** Single-contrast view, showing 5.2-cm long segment (black closed arrows) of upper thoracic esophagus with mural rigidity and nodularity, luminal narrowing, and subtle transition between normal and abnormal mucosa. **Right** Double-contrast view of same esophagus. In addition to changes seen in single-contrast view, 2-cm polypoid mass (open black arrows) can be seen along upper left side of lesion. Histologically this was infiltrating squamous-cell carcinoma with polypoid component.

frequently show some ulceration. Primary ulcerative carcinoma of the esophagus is the least common type and has received little attention in the radiologic literature (3–5).

Gloyna et al (13) described six cases of primary ulcerative carcinoma of the esophagus representing 10% of the cases they examined at M. D. Anderson Hospital and Tumor Institute over $3\frac{1}{2}$ years. The distinctive radiologic appearance of this type of tumor is that of a well-marginated, large meniscoid ulcer surrounded by a thin rind of lucency representing a collar of neoplastic tissue (Figs. 9, 10). The profile view usually shows these features to best advantage. When viewed en face the meniscoid configuration may not be apparent, although an ulcer may be seen. The appearance of a primary ulcerative esophageal carcinoma is due to ulceration of virtually all of an eccentric sessile mass. The appearance is similar to that of the better-known ulcerating gastric malignancy described by Carman (14) and Kirklin (15). Despite the presence of a large ulcerative lesion, the luminal narrowing is insignificant and the incidence of tracheo-esophageal fistula or mediastinal spread is not significantly different from conventional carcinoma.

To recognize this type of tumor, the patient should be examined in multiple projections in order to view the lesion in profile. The ulceration and the associated rim, or rind, of tumor is readily recognized. Double-contrast techniques are helpful particularly in defining the extent of the lesion.

Varicoid Carcinoma. Esophageal carcinoma with diffuse submucosal extension presenting as linear, thickened, tortuous filling defects may simulate varices both radiologically and endoscopically (Fig. 11). In observations made by fluo-

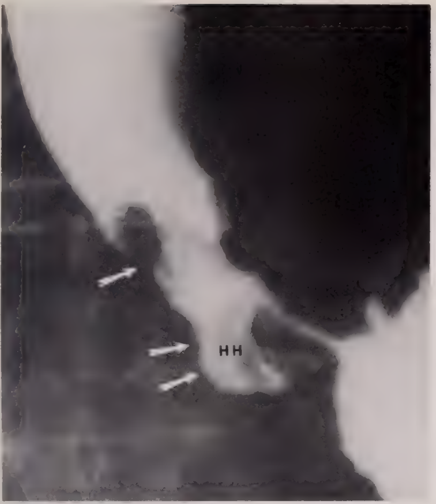


Fig. 8. A 1.5 cm polypoid tumor in distal esophagus at level of gastroesophageal junction (arrows) with infiltrative component involving associated hiatus hernia (HH). Histologically, this was adenocarcinoma, most probably arising from gastroesophageal junction.

roscopy or serial films, lack of pliability and a change in appearance with peristalsis, respiration, change in position, and Valsalva maneuvers suggest the diagnosis of carcinoma if rigidity is present, and varices if a change in shape is demonstrable. Characteristically, a varicoid carcinoma is a squamous-cell carcinoma with predominant submucosal extension. Cho et al (16) recently reported on a series of 153 patients with carcinoma of the esophagus, in which 42% showed some areas of varicoid pattern in association with other usual patterns of presentations. We believe that the true varicoid pattern as described in the literature (17–19) is a very rare manifestation of carcinoma of the esophagus. We encountered only five patients showing the varicoid pattern (Fig. 11) in the radiographs of 200 patients with carcinoma of the esophagus (incidence = 2.5%).

Lack of involvement of the distal esophagus and gastroesophageal junction is a useful distinguishing sign, since varices due to portal hypertension always involve these regions. However, "down-hill varices" from superior venacaval obstruction typically spare the distal esophagus but show the usual characteristic changing pattern during fluoroscopy. In varicoid carcinoma, submucosal infiltration causes rigidity and lack of pliability of the esophagus. If the muscular layer is involved, the peristalsis is impaired or absent. The simultaneous occurrence of a varicoid carcinoma and esophageal varices poses a particularly difficult diagnostic challenge. Careful fluoroscopic and radiographic evaluation may detect areas of noncompliance or subtle changes in the elasticity of the esophageal wall. Submucosal lymphomatous infiltration may create a varicoid pattern (20). Because of less desmoplastic reaction in lymphoma as compared to carcinoma, less rigidity as well as luminal compromise would be expected in an esophagus infiltrated by lymphoma. Diffuse nodular lesions simulating varices may also be seen in superficial spreading carcinoma (21) as well as adenocarcinoma complicating Barrett esophagus (22, 23).

Other Unusual Presentations. Carcinoma of the esophagus may simulate a smooth, tapering benign stricture. Careful analysis usually reveals subtle nodularity and an asymmetrical configuration. We encountered three such cases; one of these is illustrated (Fig. 12). Several biopsies may be necessary before a diagnosis of malignancy can be established.

Diffuse involvement of the entire esophagus by infiltrating carcinoma (Fig. 13) was seen in one patient and multiple carcinomas of the esophagus (Fig. 14) were seen in three. Widespread intraepithelial carcinoma contiguous with or independent of invasive carcinoma (24) and in association with diffuse dysplasia (25) indicates the possible multicentric origin of esophageal carcinoma. If the carcinoma is extensive in nature at the time of diagnosis despite a brief duration of clinical manifestations, this also suggests a multicentric origin (26). Yet, multiple independent carcinomas are infrequent. Moertel et al (27) reported two separate carcinomas in 10 of 421 cases of squamous cell carcinomas.

Carcinoma Complicating Chronic Achalasia. Although achalasia is considered a benign disease, its eventual course may be lethal because of complications in the late stages. The average duration of symptoms before carcinoma develops may vary from 17 to 30 years. The youngest patient reported with this combination was a 14-year-old girl (28). Disparate figures regarding the incidence of carcinoma developing in achalasia are found in the literature. These vary from 1% to 20% and average around 10%. Sanderson and Bernatz (29) in reviewing Mayo Clinic findings concluded that cancer is seen in patients with achalasia seven times more often than in the general population.

Although achalasia affects women more often

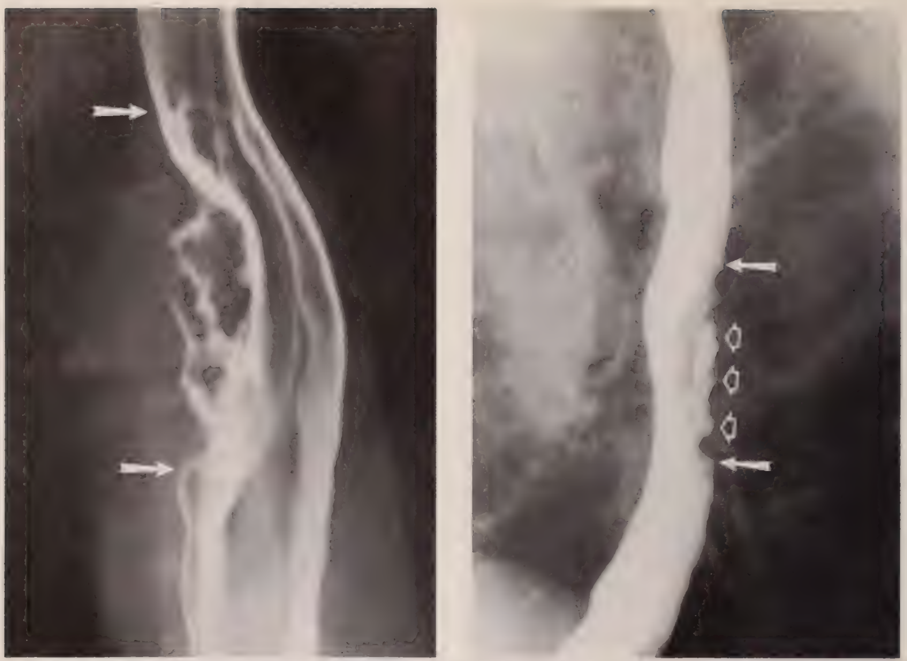


Fig. 9. **Left** Double-contrast esophagogram demonstrating primary ulcerative carcinoma in mid-esophagus. Note superior and inferior limits of tumor (arrows) consisting of sausage-shaped, large, central ulceration surrounded by rim of radiolucency, representing tumor margins. **Right** Single-contrast view, showing sausage-shaped linear ulceration (open arrows) surrounded by rim of radiolucency due to tumor. Upper and lower margins of tumor are sharply delineated (closed arrows).

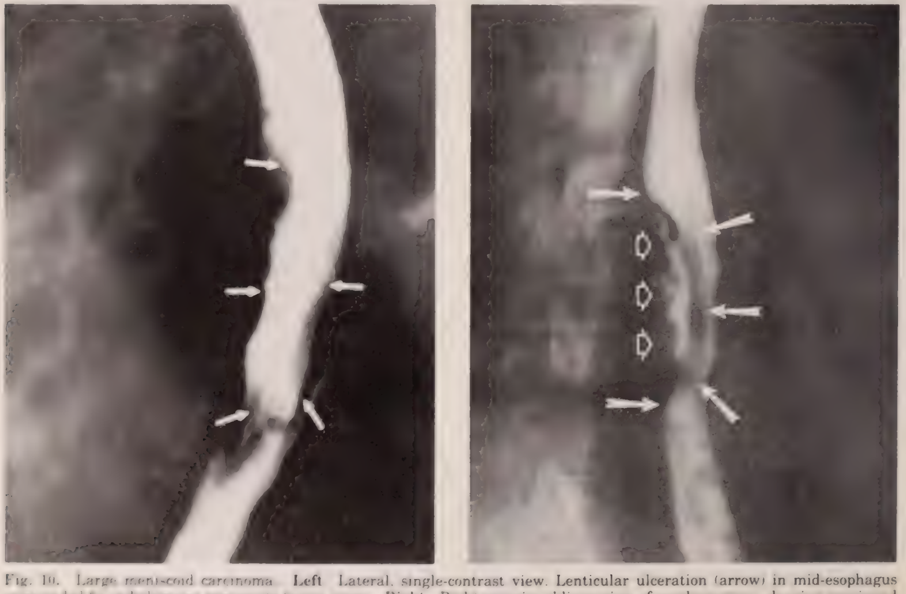
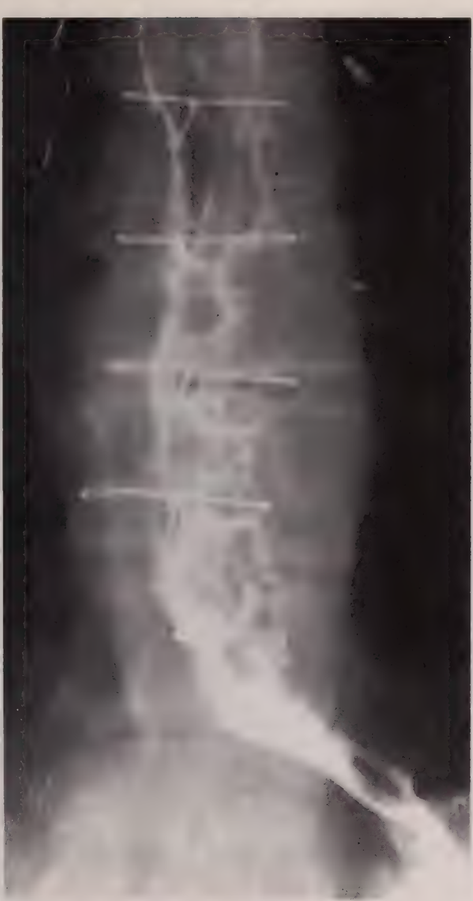


Fig. 10. Large meniscoid carcinoma **Left** Lateral, single-contrast view. Lenticular ulceration (arrow) in mid-esophagus surrounded by radiolucency represents tumor mass **Right** Right anterior oblique view of esophagogram, showing meniscoid ulcerating carcinoma; open arrows point to meniscoid ulcer. Closed arrow outlines surrounding tumor mass as well as upper and lower margins of tumor



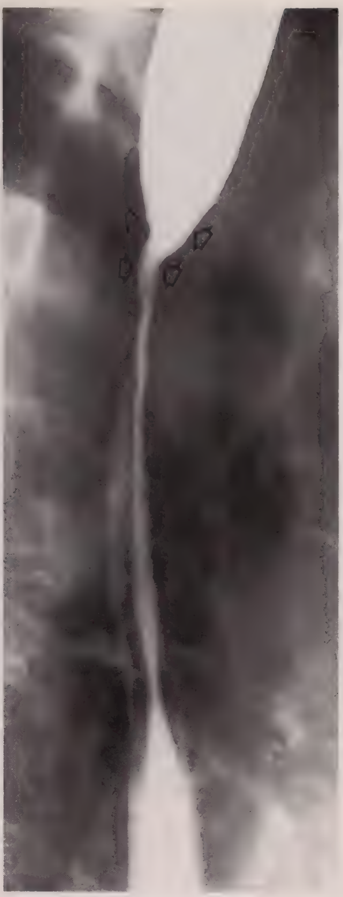
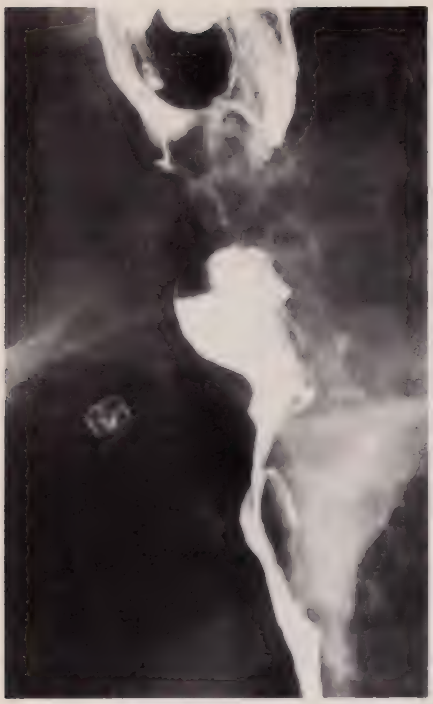


Fig. 11. Left Extensive varicoid carcinoma simulating varices involving lower half of esophagus. Histologically, this was adenocarcinoma arising in Barrett's esophagus.

Fig. 12. Right Smooth tapering stricture in upper thoracic esophagus (arrows), with "jet phenomenon" simulating benign stricture. Short length of stricture, minimal nodularity along posterior wall, and lack of displacement were indications of malignancy. Histologic diagnosis was infiltrating squamous-cell carcinoma.

than men, carcinoma appears three times more frequently in male patients afflicted with achalasia. Carcinoma also appears at an earlier age in the esophagus with achalasia than in the normal esophagus, the average age in the former instance being 48 years, as opposed to an average age of 64 years if the esophagus is normal (30); and many patients may be younger than 40 years. Although carcinoma may arise at any level of the esophagus with achalasia, its preferred site is the middle third. Most reports incriminate squamous-cell carcinoma as the most common malignant tumor complicating achalasia (31). It is often described as being extensive and polypoid or cauliflower in form. Other histologic types, such as adenocarcinoma, undifferentiated carcinoma, and carcinosarcomas, have also been described (30). The malignant tumor is localized ini-



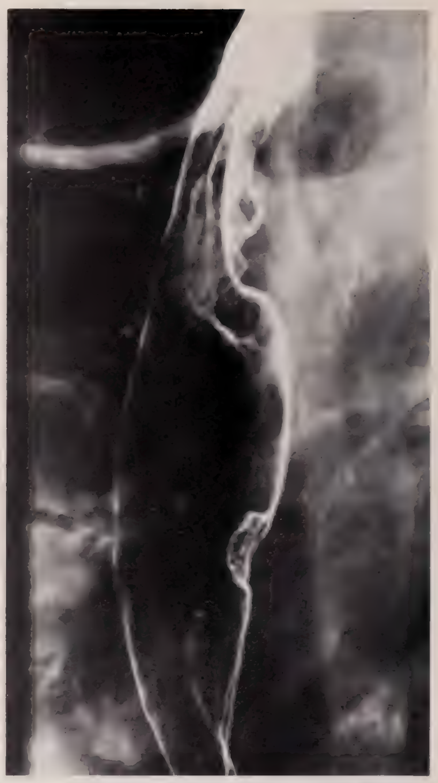


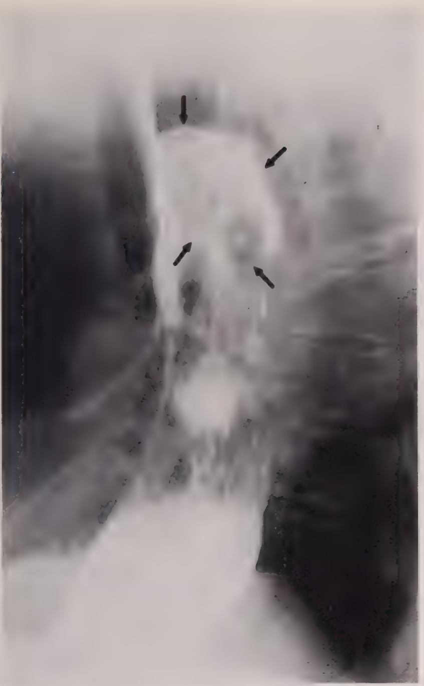
Fig. 13. Diffuse infiltrating carcinoma of esophagus. Esophagogram of 66-year-old woman, showing diffuse, irregular narrowing and marginal nodularity of esophagus wall. Biopsy revealed diffuse infiltrating squamous-cell carcinoma. Patient underwent total transhiatal esophagectomy and pharyngogastric anastomosis.

Fig. 14. Multiple carcinomas. Double-contrast esophagogram, showing multiple polypoid tumors in esophagus. Histologic diagnosis was squamous-cell carcinoma. Patient underwent transhiatal esophagectomy and cervical esophagogastrostomy.

tially, typically remains undetected for a long period of time, and metastasizes. It spreads throughout the esophagus and has a marked tendency to invade by extension in the submucosa. The tumor is apt to leave the esophagus and invade mediastinal structures. Tracheoesophageal fistula may develop as a terminal stage. Perforation of the esophagus with resulting pneumothorax, empyema, or pulmonary abscess may occur, and perforation of the aorta with massive bleeding can constitute the terminal event.

Radiologic identification of carcinoma developing in chronic achalasia poses a particular problem. Because of retention of fluid and food, the carcinoma may be difficult to detect.

Esophageal lavage should be used, if necessary, to cleanse the esophagus prior to radiologic study. Under these conditions, in patients with partial esophageal obstruction and absence of peristalsis, a good double-contrast esophagogram is easily obtained. Patients with long-standing achalasia should have regular esophagograms to facilitate the early detection of carcinoma. Typically, a large polypoid squamous-cell carcinoma arises in the middle third of the esophagus. We encountered two patients with achalasia complicated by development of carcinoma, one with a large polypoid tumor in the mid-esophagus and the second with extensive carcinoma and bronchoesophageal fistula (Figs. 15, 16).



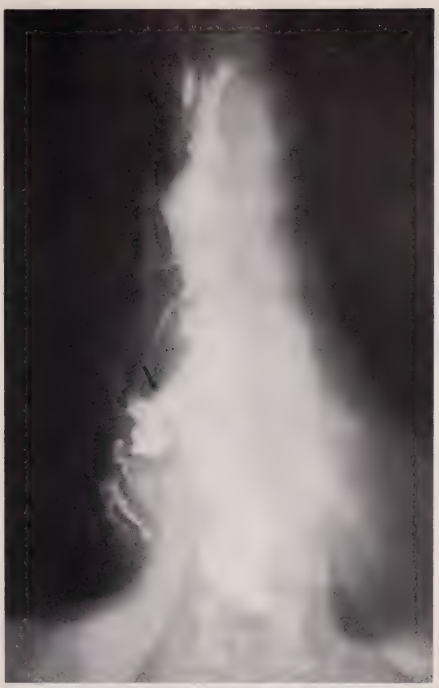
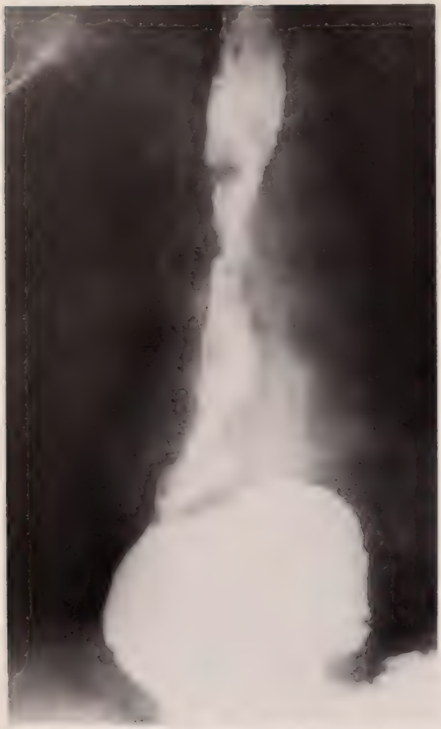


Fig. 15. Left This 66-year-old man with chronic achalasia complained of recent increase in dysphagia and weight loss. Esophagogram demonstrates large polypoid mass in midthoracic esophagus (arrows). Diagnosis is difficult because of chronic dilation and retention of food and secretions in the esophagus. Biopsy of lesion revealed well-differentiated squamous-cell carcinoma.

Fig. 16. Right This 69-year-old woman had long-standing chronic achalasia, with recent increase in dysphagia and recurrent respiratory symptoms. Large polypoid and infiltrating mass in middle third of esophagus; Esophagobronchial fistula (arrow) between right lower lobe bronchus and esophagus. Note underlying typical changes of achalasia.

Carcinoma Complicating Barrett Esophagus. Extensive columnar metaplasia of the distal esophagus or a columnar-lined lower esophagus represents a late, irreversible stage of peptic reflux esophagitis. The premalignant character of this condition has been established by an 8.5% incidence of adenocarcinoma in a series of 140 cases of Barrett esophagus reported by Naef et al (32). Perhaps the first well-documented instance of adenocarcinoma occurring in a Barrett esophagus was that reported by Morson and Belcher (33). The tumor was situated in the mid-esophagus about the level of tracheal bifurcation. The mucous membrane above the tumor was entirely squamous, and that below the lesion was mostly glandular, apart from a few islands of squamous epithelium. In a review of 94 instances of adenocarcinoma occurring in Barrett esophagus (34), 62 were noted to be associated with hiatus hernia. Sixty-two instances of carcinoma were located in the middle third of the esophagus, 30 in the lower third, and two at the junction of the middle and lower thirds. The average size of the lesion was 4.3 cm, with a range of 1.0 to 9.0 cm. The classic radiologic features of Barrett esophagus usually consist of a hiatus hernia, short midesophageal stricture, and ulcer and gastroesophageal reflux (35). Recently, however, Robbins et al (36, 37) found that strictures are actually more common in the distal esophagus, and that the majority of cases do not fit the classic stereotype of a high esophageal stricture or ulcer. Therefore, it has been difficult to diagnose this entity radiologically, and a definitive diagnosis has depended upon histologic verification of a columnar epithelial lining in the esophagus. More recently,



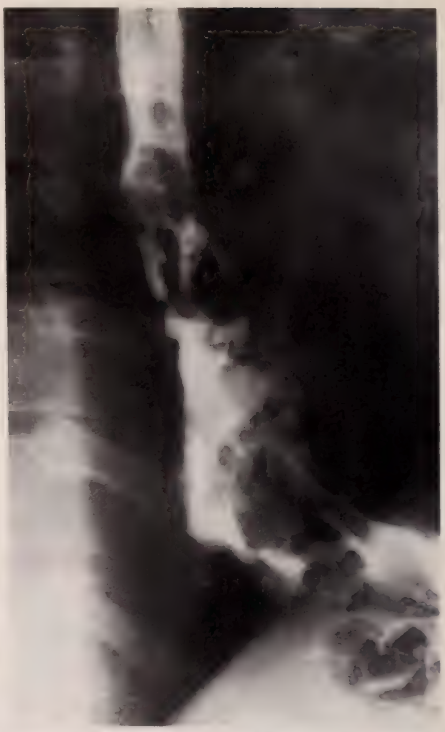


Fig. 17. **Left** Adenocarcinoma arising in Barrett esophagus. Esphagogram showing large hiatus hernia, extensive contour irregularity, and varicoid appearance of lower two-thirds of esophagus.

Fig. 18. **Right** Adenocarcinoma complicating Barrett esophagus. Esophagogram showing hiatus hernia and varicoid appearance of lower third of esophagus.

Levine et al (38) have described a reticular pattern of mucosa in Barrett esophagus seen in 7 cases in a series of 29 cases (24%) and have suggested that it represents a specific radiologic sign of Barrett esophagus. In this review, we encountered 23 adenocarcinomas complicating Barrett esophagus. The diagnosis of carcinoma complicating Barrett esophagus does not lend itself to early diagnosis short of biopsy, unless radiologically it is an advanced tumor. We have also seen a varicoid pattern in Barrett esophagus complicated by adenocarcinoma in two patients (Figs. 17, 18).

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Adenocarcinoma Arising in Barrett Esophagus: Pathologic and Radiologic Features

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Abstract

We studied 17 patients with adenocarcinoma arising in the esophageal columnar epithelium or the Barrett esophagus. We applied strict pathologic criteria to ascertain that the adenocarcinoma arose from the columnar-lined esophagus rather than the stomach. These were:

1. Adequate description of the gross specimen, with documentation of the specific sites from which tissue sections were obtained.
2. Identification of esophageal mucosa by characteristic mucus-secreting glands or ducts.
3. The presence of benign columnar mucosa lining the esophagus adjacent to or surrounding adenocarcinoma.
4. The presence of benign columnar or normal esophageal mucosa between the cancer and gastric epithelium.

Adenocarcinoma arising from columnar-lined esophagus is radiographically indistinguishable from adenocarcinoma of gastric origin and squamous-cell carcinoma of the esophagus.

The incidence of adenocarcinoma of the esophagus is estimated to be between 1% and 19% (1, 2). Although up to 76% of these tumors are of gastric origin, the remainder arise predominantly from esophageal columnar or Barrett epithelium. Rarely, primary adenocarcinomas may also originate from esophageal mucus-secreting glands. A few such cases have been reported (3–5).

This series constitutes one of the largest of adenocarcinomas of the esophagus reported in the radiologic literature and is characterized by the use of strict pathologic criteria which assure origin of the tumors from esophageal columnar epithelium rather than gastric mucosa. Grossly, adenocarcinoma of the esophagus is indistinguishable from the squamous cell variety and, when the esophagogastric junction is involved, there is no radiologic means of differentiating between gastric and esophageal tumors. In each instance the prognosis is the same for tumors of a similar stage. However, columnarization of the esophageal epithelium is frequently associated with demonstrable radiologic abnormalities, and the associated histologic changes may be precursors of malignancy. Radiologists should be familiar with the sequence of events if preventive treatment is to be successful.

Materials and Methods

The records and roentgenograms of all patients seen at M. D. Anderson Hospital between 1963 and 1983 with the discharge diagnosis of adenocarcinoma arising from Barrett epithelium were reviewed. A portion of the patient population was identified by search of the data base of the Department of Patient Studies.

Tissue slides obtained from biopsy and surgical specimens were examined (by JLS). Gross and mi-

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croscopic criteria of adenocarcinoma arising from columnar-lined esophagus were evolved and strictly applied. These were:

- A precise gross description of the specimen with documentation of the specific sites from which tissue sections were obtained.
- Identification of esophageal mucosa by characteristic mucus-secreting glands or ducts.
- The presence of benign columnar mucosa lining the esophagus adjacent to or surrounding adenocarcinoma.
- The presence of benign columnar or normal esophageal mucosa between the cancer and gastric epithelium.

All available esophagrams were reviewed (by GDD & SJK). Single contrast studies were employed for the earlier cases. More recent examinations included double contrast techniques.

A total of 113 patients with the discharge diagnosis of adenocarcinoma arising in esophageal columnar epithelium were identified. Only 17 of these (15%) had clear-cut histologic characteristics which permitted the diagnosis of adenocarcinoma arising in Barrett epithelium also having x-rays available for review purposes. Thirty (26.6%) were found to have adenocarcinoma originating in the stomach. The remaining 66 (58.4%) patients were classified as having adenocarcinoma of indeterminate origin, either because the tissue sample was inadequate or because the biopsy site was uncertain.

The demographic and pathologic features of the patients with unequivocal adenocarcinoma originating in a columnar-lined esophagus included an age range of 37 to 84 years of age (mean, 59 years). Only one of the 17 patients was female.

A total of 5 patients had other associated primary tumors. Three were of head and neck origin (vocal cord, simultaneous; larynx, 3 years later; and tonsil $1^{1}/_{2}$ years later) and the remainder arose from the skin (melanoma, chin, developed 5 months later; and simultaneous basal-cell carcinoma, left postauricular).

Patient Findings

The reputedly classic radiographic findings in Barrett esophagus include stricture in association with peptic ulceration and hiatus hernia. The stricture is usually described as being atypical in location, i.e. the middle third of the esophagus (6–8). In the current series, as well as in a review of the literature, hiatal hernia was the most frequent associated finding—in 75% of reported cases and in 64.7% of the patients in this series (Table 1). Benign esophageal stricture was next most frequent, occurring in 64.3% of cases in the literature. Gastroesophageal reflux and severe esophagitis were seen in slightly less than half of the compiled cases of esophageal columnar epithelium, with mucosal ulceration observed in approximately one-third of the cases. In the current

TABLE 1
Radiographic Features Associated with Barrett Esophagus

Ref. No.	Hiatal Hernia	Reflux	Benign Stricture	Esophagitis	Peptic ulcer	Other	Total Pts
2	9	5					17
7	20	16	21	18	14	8*/1†	26
8	33	24	32	29	21		39
9			8	4	2		14
10	11	3	5		4		11
11	5	3				3*	5
12			2		1		2
13	26	13	24	14		7‡	29
14	2	2	2	1			2
15	20		14		9		23
TOTAL:	126 (75%)	66 (39.3%)	108 (64.3%)	66 (39.3%)	51 (30.4%)	11*(6.6%) 1†(0.6%) 7‡(4.2%)	168 (100%)
Current series:	11 (64.7%)	2§ (11.8%)					17 (100%)

* Duodenal ulcer.

† Antral ulcer.

‡ Reticular mucosa.

§ Reflux by history (not seen) associated with hiatal hernia in one patient; reflux demonstrated without associated hiatal hernia in another patient.

series, 1 patient demonstrated gastroesophageal reflux with no radiographic confirmation and, among the other patients, either no reflux was demonstrated or no statement concerning reflux was made on the dictated report. There were associated duodenal or antral ulcers in 7.2% of cases compiled from the literature. None were encountered in the present series. Recently, Levine et al, using double contrast techniques, have demonstrated a delicate reticular mucosal pattern in approximately one third of patients with proven Barrett esophagus (13). This is associated with villous metaplasia and is considered highly specific by the authors.

TABLE 2

Radiographic Features of Adenocarcinoma Arising in Columnar-Lined Esophagus

Pt No.	Mass Characteristics	Ulcer	Obstruction	Location in Esophagus
1	Predominantly infiltrative		Moderate	EG junction
2	Infiltrative	+	Marked	EG junction
3	Exophytic and infiltrative			Mid
4	Infiltrative		Marked	EG junction
5	Infiltrative		Marked	Mid
6	Exophytic and infiltrative			Mid
7	Predominantly infiltrative			EG junction
8	Infiltrative	+		Distal
9	Exophytic		Slight	EG junction
10	Infiltrative			Mid
11	Exophytic	+	Moderate	Mid & distal
12	Exophytic			Mid & distal
13	Predominantly infiltrative	+	Moderate	EG junction
14	Infiltrative	+	Moderate	EG junction
15	Exophytic	+		EG junction
16	Exophytic	+		Proximal
17	Infiltrative	+		EG junction

Despite the often-repeated statement that Barrett epithelium is prone to occur in the middle third of the esophagus, involvement of the esophagogastric junction is more common. In this series (Table 2), 9 of the adenocarcinomas arose from the region of the EG junction (Fig. 1). Only 1 was seen in the proximal esophagus (Fig. 2), 4 in the mid esophagus (Fig. 3), 2 at the junction between the mid and distal esophageal segments, and 1 in the distal esophagus above the EG junction. Radiographically demonstrable tumor was present in all cases. For descriptive purposes the tumors were characterized as exophytic, that is, with a bulky intraluminal component (Fig. 4), or infiltrative, i.e. with submucosal mass and ri-

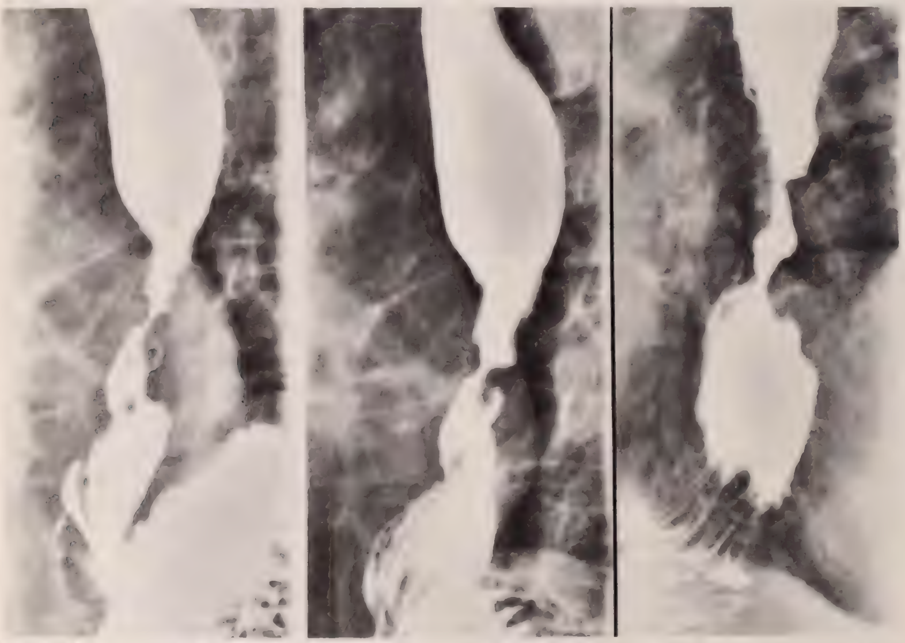


Fig. 1. Adenocarcinoma of esophagus (patient 13). Predominantly infiltrative mass, with exophytic components, causing moderate esophageal obstruction.

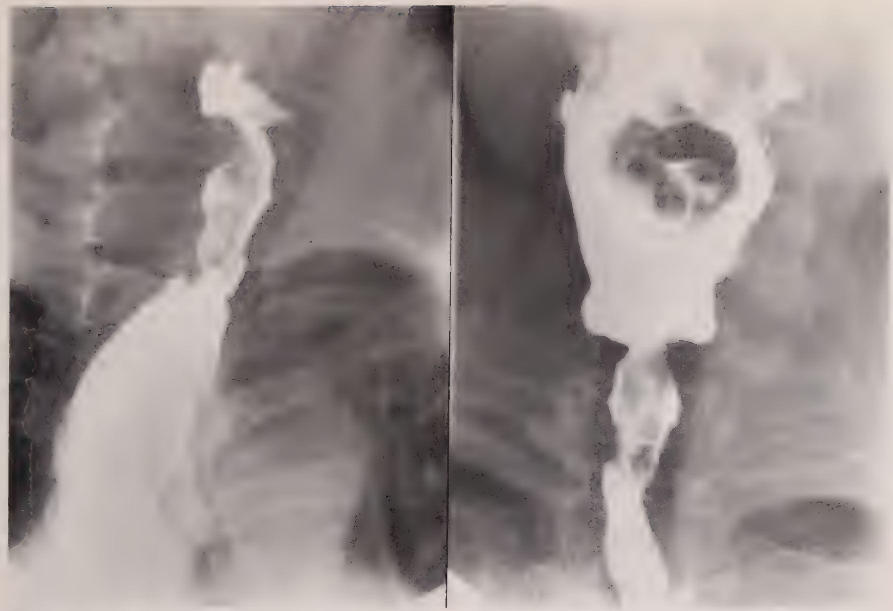


Fig. 2. The only case of adenocarcinoma arising from proximal esophagus observed in this series (patient 16). Note exophytic, ulcerated mass.

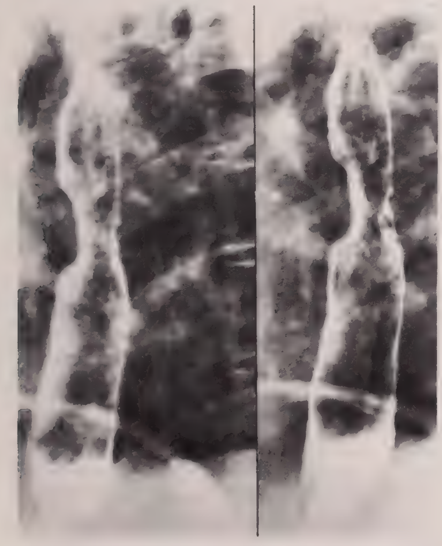


Fig. 3. Infiltrative adenocarcinoma involving mid and distal esophagus (patient 10).

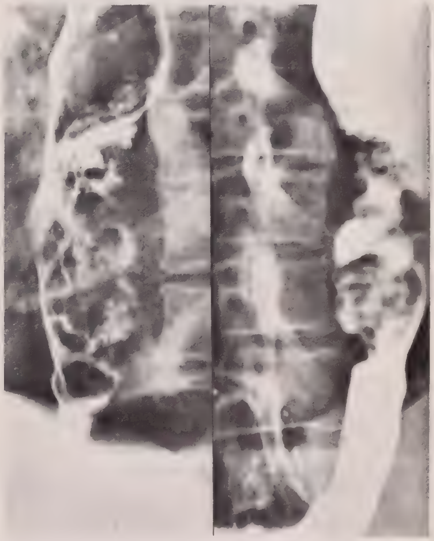


Fig. 4. Intraluminal, ulcerating adenocarcinoma involving mid and distal esophagus (patient 11).

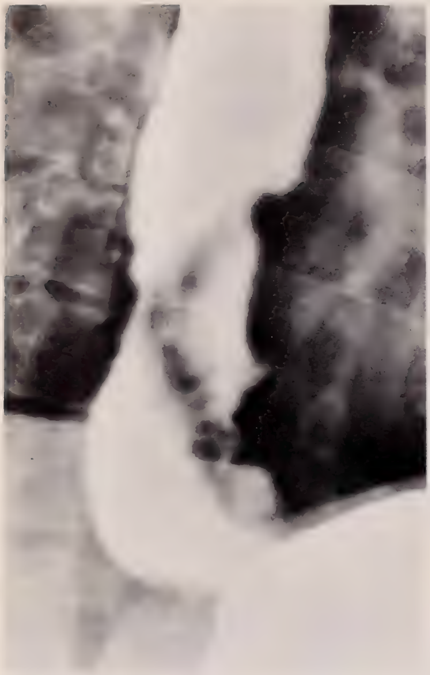


Fig. 5. A classic Carman-Kirklin complex occurring in an exophytic mass at EG junction (patient 15).

gidity. Most patients (10/17) demonstrated predominantly or totally infiltrative disease (Table 2). In 2 patients the tumor masses had equally exophytic and infiltrative features, and in 5 patients, the masses were primarily exophytic. Ulceration of the mass lesions was noted in 8 patients (Fig. 5, 6). Marked esophageal obstruction was present in 3 patients, moderate in 4 and slight in 1.

Only 4 of the 17 patients in this series are presently alive, the survival times ranging from 7 months to 4 years following diagnosis (Table 3). Among those who died, the mean survival following diagnosis was 11 months (range, 4–20 months). The immediate cause of death was not specified in 7 patients. In 5 patients, death was related to widespread metastases. One patient died of pneumonia. All but 1 of the patients underwent esophagectomy or esophagogastrectomy, either alone (5 patients) or in combination with external beam irradiation (5 patients), chemotherapy (2 patients), or both (4 patients). The patient who was not treated surgically received radiation and chemotherapy.

Discussion

Columnar-lined esophagus, also known as Barrett epithelium, was first described in 1950 (16). Barrett originally believed that a congenitally short esophagus explained the presence of the gastric type mucosa. However, Allison and Johnstone (1953) established that esophageal columnar epithelium is, in fact, of esophageal origin (17). Although there has been debate about the congenital (18, 19) vs. acquired (20) etiology of this entity, most recent evidence favors the acquired theory (4, 15, 21). Barrett esophagus is presumed to represent columnar metaplasia of squamous epithelium as the result of reflux esophagitis.

Descriptions of the pathology of columnar-lined esophagus vary. Paull et al (10) described an orderly progression of cell types consisting of parietal and chief cells ("gastric type") located most distally, cardiac and mucous glands centrally ("fundic type") and villiform intestinal-type goblet cells ("specialized type") proximally. Thompson et al (22) did not discern any zonation of Barrett epithelium. By contrast, these authors noted a complex mixture of the various cell types and architectures. Thompson's observations are more in keeping with our experience. Indeed, any reason for the zonation Paull described is inapparent.

Patients with columnar-lined esophagus are at increased risk for the development of adenocarcinoma (15, 23). In the largest series of patients, Naef et al reported adenocarcinoma in 12 (8.6%) of 140 patients (23). Others have reported an incidence of up to 46% (15). Adenocarcinoma has also been noted in patients with Barrett esophagus in association with scleroderma (12, 24), achalasia (25), and the Zollinger-Ellison syndrome (26). Obviously, the exact incidence has not been determined and, as noted by Margulis (27), the incidence of Barrett epithelium is substantially higher than that of superimposed adenocarcinoma. While surveillance with endoscopy and biopsy and/or brush cytology has been recommended for follow-up patients with proven esophageal columnar metaplasia (2, 23, 28), it is probable that many cases of Barrett epithelium are not recognized and adenocarcinoma never develops. In patients with severe gastroesophageal reflux and columnar changes Skinner et al (15) support the use of antireflux surgery to prevent the development of dysplasia and adenocarcinoma. Regression of the epithelial change has been reported in instances. In addition, prophylactic esophagogastrectomy is suggested for those patients with high-grade dysplasia.

TABLE 3

Adenocarcinoma Arising in Barrett Esophagus: Treatment and Follow-Up

Pt. No.	Therapy*	Survival†	Cause death‡	Complications
1	S, XRT, Ch	17 mos.	Pneumonia	Metastases: lymph nodes, spine
2	S, XRT, Ch	12 mos.	Not specified	Perforation S/P initial endoscopy
3	S	Alive 2 yrs PD		Bone metastases
4	S	Alive 20 mos PD		Chylothorax postop
5	S, XRT	Alive 7 mos PD		Paralysis (L) vocal cord postop Sinus midsternum
6	Si, XRT	Alive 4 yrs PD		Pulmonary embolism postop
7	S	5 mos.	Not specified	Recurrent pleural effusion
8	S, XRT_m, Ch	20 mos.	Not specified	MI interrupted Ch
9	S, Ch	5 mos.	Wide met	
10	S, Ch	14 mos.	Wide met	
11	S, XRT	4 mos.	Wide met (emaciation, dehydration)	
12	S, XRT, Ch	13 mos.	Wide met	
13	S	7 mos.	Not specified	
14	S, XRT	16 mos.	Wide met	Recurrence
15	S, XRT	14 mos.	Not specified	Recurrence Bone metastases
16	Si, S	5 mos.	Not specified	Metastases: cervical lymph nodes
17	XRT, Ch	12 mos.	Not specified	Metastases: periportal lymph nodes with jaundice

* S = surgery (esophagogastrectomy), Si = colonic interposition, XRT = radiation therapy, XRT_m = palliative radiation to metastases, Ch = adjuvant chemotherapy.

† PD = post diagnosis.

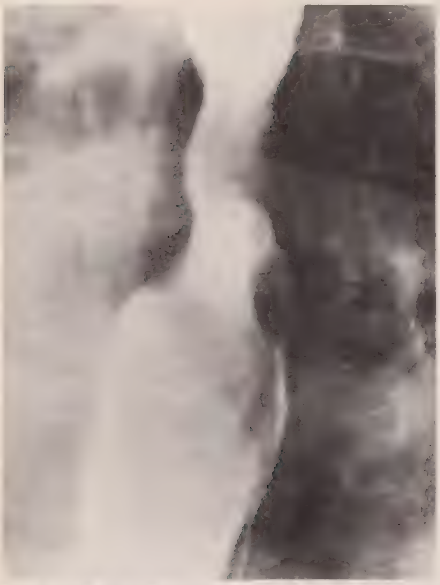
‡ Wide met = widespread metastases.

In order to distinguish between adenocarcinomas arising in the distal esophagus from columnar epithelium and those of gastric origin, strict pathologic criteria must be applied; the two entities are indistinguishable radiographically. This distinction was not clearly defined in the study of Levine et al (2) which included carcinomas involving the EG junction which also showed adjacent esophageal columnar metaplasia. Skinner et al (15) advocate the use of gross morphologic criteria. That is, they defined Barrett esophagus as 3 cm or more of distal tubular esophagus lined by columnar-type epithelium. In the current series, the microsopic pathologic criteria described by Smith (3) were used in addition to gross criteria. We believe this combination is more precise in the recognition of small foci of columnar-lined esophagus and the separation of tumors of gastric and esophageal origin.

Our investigation of 113 patients with the purported diagnosis of adenocarcinoma arising in columnar-lined esophagus resulted in only 17 confirmed cases. The precise origin of adenocarcinoma could not be ascertained in the majority (66), due to insufficient tissue for pathologic analysis or uncertainty concerning the exact location of the biopsy site. However, in view of the hypothesis by Levine et al (2) which suggests that the majority of cases involving the EG junction develop on the basis of Barrett esophagus, it is noteworthy that 30 of our cases clearly were of fundal origin or 1.7 times the incidence of adenocarcinoma arising in the esophagus. Therefore, when the distinction between adenocarcinoma arising from Barrett epithelium and that of gastric origin is sought, sufficient tissue from a carefully described location is essential.

In this series, all but one of the patients with adenocarcinoma arising in esophageal columnar epithelium were male. Skinner et al (15) observed a similar sex distribution: 18 of their 20 patients were male. In the general literature, approximately 2/3 of cases of adenocarcinoma with Barrett esophagus occurred in males (29).

The mean age in our series of patients with adenocarcinoma arising from columnar-lined esophagus was 59 years. This is remarkably close to the mean age of 60 years observed by Skinner et al (14), Haggitt et al (4), Witt et al (28), and Levine et al (2).



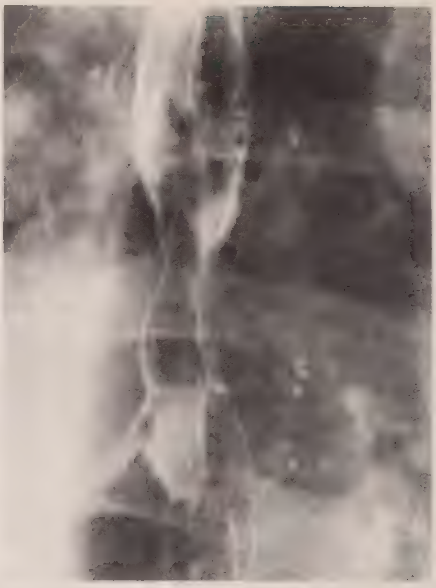


Fig. 6. Left Superficial ulceration in an infiltrative plaquelike adenocarcinoma at EG junction (patient 17).

Fig. 7. Right Squamous cell carcinoma arising from EG junction radiographically indistinguishable from adenocarcinoma in this region (see Fig. 6).

Adenocarcinomas originating in esophageal columnar epithelium have been reported in the proximal (28), mid (30–33), and distal (2, 34) esophagus. As in other series, the majority of our 17 cases arose from the EG junction or distal and mid esophagus, with only one arising from the proximal third. Those occurring in the distal third or at the EG junction commonly cannot be distinguished from gastric cancer; a clear zone of non-malignant demarcation between the esophagus and stomach is frequently difficult to discern.

Masses were observed on the esophagrams of all our patients. As in the series of Levine et al (2), these were predominantly infiltrative (10/17 patients). Ulcerated masses were noted in almost half of the patients, as was complete or partial esophageal obstruction. Therefore, above the EG junction, there are no radiographic features that can distinguish adenocarcinoma from squamous cell cancer of the esophagus (Fig. 7).

Head and neck malignancies developed in 3 patients in our series, either before or synchronously with the esophageal primary. This is in keeping with Goldstein and Zornoza's (35) observation of a dramatically higher incidence of esophageal carcinoma in association with squamous cell carcinoma of the head and neck region. Two additional patients had skin malignancies.

The prognosis of patients with esophageal adenocarcinoma is poor. Review of the literature reveals an average survival of approximately 10 months among those treated by external beam irradiation with (35, 37) or without (9, 36, 41) surgery. Among those treated with surgery alone there was approximately a 40% mortality (4, 5, 7, 14, 29, 32, 34, 36–41) in the first year following surgery, although 5-year survivals of up to 24% (42) have been reported. Only 4 patients in the present series are alive 7 months to 4 years following initial diagnosis. The average survival of the 13 patients who died was 11 months.

In light of the poor prognosis, prevention and early identification of adenocarcinoma arising in Barrett epithelium is warranted. The problem of identification of Barrett epithelium has been lessened by the demonstration of a characteristic mucosal pattern by Levine et al (13). This may be seen in about one-third of patients with columnar dysplasia and is apparently related to a villous component. While the suggestion that the villous changes may be associated with a high malignant potential is unproven, in our series of adenocarcinomas adjacent villous metaplasia was common and the malignant potential of villous tumors elsewhere in the gastrointestinal tract is well-established. Therefore, even though routine endoscopy may not be practical except in the most severe cases of reflux esophagitis, the possibility that those at risk may be identified by routine double contrast esophagography should be intensively investigated.

Strict pathologic criteria are necessary for the accurate diagnosis of adenocarcinoma arising from Barrett epithelium. This requires adequate tissue sampling and documentation of the sample's origin.

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Steroid-Responsive Dysphagia: A Clue to the Diagnosis of Esophageal Lymphoma

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Abstract

> Listen to the patient. He is telling you the diagnosis.
>
> Hermann L. Blumgart, M.D.
> Late Professor of Medicine Emeritus
> Harvard Medical School

We report an unusual case of primary histiocytic lymphoma of the esophagus without extraesophageal involvement. The patient reported having "asthma" and dysphagia for 16 months. Although a midesophageal lesion was found that appeared carcinomatous on both x-ray and endoscopy, the first clue to the correct diagnosis lay in the patient's history of consistent responsiveness of his dysphagia to repeated courses of prednisone. The patient has achieved long-term remission on radiotherapy and chemotherapy alone.

The commonest primary malignancy of the esophagus is squamous cell carcinoma, and the commonest presenting symptom of this disease is progressive dysphagia (1). Rarely, non-Hodgkin's lymphoma may present in the esophagus, and the presenting symptoms are similarly those of dysphagia and weight loss. In most cases, the rarity of primary esophageal lymphoma militates against suspecting the diagnosis. We present a case of primary histiocytic lymphoma of the esophagus in which the presenting history of steroid-responsive dysphagia provided the first clue to the nature of the lesion despite "classic" radiographic and endoscopic appearances of carcinoma.

Case Report

A 61-year-old man, a physician, was admitted to The Mount Sinai Hospital for evaluation of progressive dysphagia. He had been entirely well until sixteen months prior to admission, when he noted the onset of wheezing. His chest x-ray was normal. He was told by his local physician that he had "asthma" and he was treated with tetracycline and theophylline. There was no improvement in his symptoms, so prednisone (40 mg/day) was added to the regimen, and the wheezing promptly abated. During the ensuing sixteen months, the patient medicated himself with tetracycline almost continuously, while the steroid medication was tapered and then discontinued.

Ten months prior to admission, the patient first noted the onset of dysphagia for solid food and concomitant worsening of his asthma. Steroids were reinstituted at 40 mg/day, and the bronchospasm and dysphagia remitted simultaneously. As the steroids were tapered, however, the dysphagia returned. Over the next nine months, occasional bouts of bronchospasm prompted resumption of the use of prednisone. Each time the patient was placed on prednisone, 40 mg/day, his dysphagia disappeared, only to reappear with tapering of the steroid dose. At a maintenance dose of 10 mg/day, there was no wheezing, but the dysphagia worsened.

Three weeks prior to admission, an upper gastrointestinal series revealed a nodular, ulcerated stricture in the midesophagus (Fig. 1). Upon visual inspection by fiberoptic endoscopy at another hospital, the lesion looked like carcinoma, but all biopsies were negative. By this time, the patient

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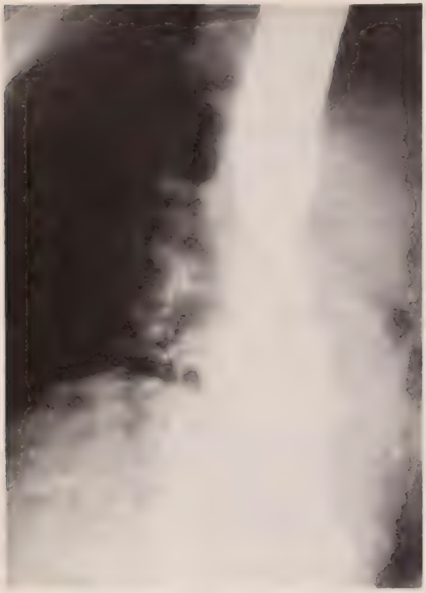

Fig. 1. Initial upper-GI series, showing nodular, ulcerated stricture in midesophagus.

could tolerate only liquids, and he was transferred to The Mount Sinai Hospital for possible surgery.

His medical history was otherwise negative; however, his father had died of esophageal carcinoma. The patient felt generally quite well and was only mildly anorectic. He denied experiencing fever, chills, sweats, weight loss, or skin rash.

The patient was not cachectic and his physical examination was normal. Laboratory data were also unremarkable: WBC count, 8800 per cu mm; normal differential; hematocrit 37%, MCV 81 fl; and platelet count, 344,000 per cu mm. SMA-6 and SMA-12 were also normal except for a slightly elevated alkaline phosphatase (114 I.U., normal up to 90). Prothrombin time was minimally elevated to 14/12 seconds, and was corrected with vitamin K.

Computerized tomographic scans confirmed the presence of a circumferential mass in the esophageal wall (Fig. 2); the rest of the mediastinum and the abdomen were normal. Repeated upper endoscopy demonstrated nodular, friable, heaped-up mucosa with ulcers and exudate; biopsy and brushings yielded only cellular debris and ulcerated but otherwise normal mucosa.

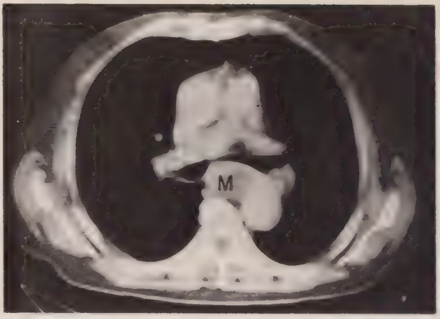

Fig. 2. CT scan, showing isolated circumferential mass (M) in esophageal wall.

Because of the consistent steroid-responsiveness of the dysphagia over a 16-month course, without the development of either total obstruction or cachexia, the possibilities of lymphoma or benign inflammatory process (perhaps secondary to tetracycline) were postulated. Rigid esophagoscopy and deep esophageal biopsy were therefore carried out. The biopsy material taken at 21 cm and 27 cm revealed a diffuse non-Hodgkin's lymphoma composed of both large cleaved and noncleaved atypical lymphoid cells (Fig. 3). The lymphoma was classified as diffuse "histiocytic" by the Rappaport classification (2), and as diffuse large cell malignant lymphoma, intermediate grade, by the new Working Formulation of non-Hodgkin's lymphomas (3). The tumor involved the submucosa and muscularis externa, and was covered by intact squamous mucosa, presumably accounting for the previous negative biopsies.

Bronchoscopy, liver-spleen scan, abdominal ultrasound, and bone-marrow aspirate and biopsy were all negative. Radiotherapy was delivered to the mediastinum in a dose of 3500 rads over four weeks with coverage by high-dose prednisone, followed by six months of chemotherapy with prednisone, cyclophosphamide, and vincristine. Twelve months after completing this treatment, the patient was feeling perfectly well, without any additional medication, and was eating normally. Repeated upper GI series (Fig. 4) and esophagoscopy demonstrated no residual disease.

Discussion

The gastrointestinal tract is the most common site of primary extranodal lymphoma (4). It is also a frequent site of disseminated nodal disease, with up to 10% of patients having intestinal involvement at some point in the course of their

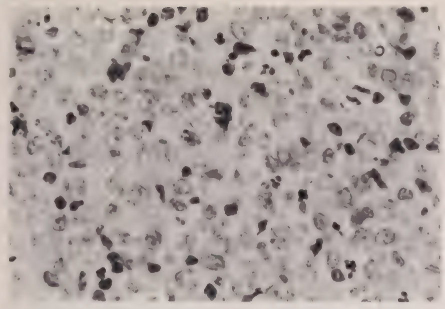

Fig. 3. Esophageal biopsy showing diffuse large cell lymphoma (hematoxylin and eosin, original magnification 400×).

illness (1, 5). In all published series, most primary gastrointestinal lymphomas are in the stomach or small bowel. The esophagus is the hollow viscus least commonly involved in either primary or disseminated disease, with reported frequencies always less than 2% (6–8). Indeed, since the usual location for esophageal lymphoma is contiguous with the stomach (9), many of these cases may actually represent proximal extension of gastric lymphoma, a far more common lesion. In all the series mentioned (4–9), whether the tumor is primary in the gastrointestinal tract or secondary to disseminated involvement by lymphoma arising elsewhere, the most common histologic subtype is that of diffuse histiocytic lymphoma.

It is extremely rare for the esophagus to be the only site of malignant lymphoma. Even in cases presenting initially with esophageal involvement, extraintestinal foci have usually been found in the bone marrow, trachea, paratracheal nodes (10), scalene fat pad, or in a periumbilical subcutaneous mass (11). There is only one published report of isolated esophageal lymphoma (1), and in that case bone-marrow examination was not described.

The differential diagnosis between carcinoma and lymphoma has profound prognostic and therapeutic implications. Carcinoma, even when treatable by surgery and/or radiotherapy, carries a uniformly bleak prognosis, but treatment of lymphoma by radiation, surgery, and/or chemotherapy often produces remarkable results (5, 11, 12). Clinically, however, the differential diagnosis is difficult.

As with carcinoma, patients with esophageal lymphoma may present with dysphagia, anorexia, weight loss, or epigastric pain. Even so-called "secondary achalasia" has been reported with both carcinoma and lymphoma (13). The radiographic appearance of lymphomas is also variable. Ulcerated and nonulcerated polypoid masses, ulcerated stenoses, "pseudoachalasia," multiple submucosal nodules, and a "varicoid" pattern have all been described (9, 12, 13). Endoscopically, the mucosa overlying a lymphoma is usually intact, albeit erythematous and friable, so that the diagnosis may not be readily established by flexible endoscopic biopsy. With carcinoma, by contrast, the more typical necrotic, ulcerated, heaped-up character of the tumor can be appreciated, and even a superficial biopsy is more likely to be positive.

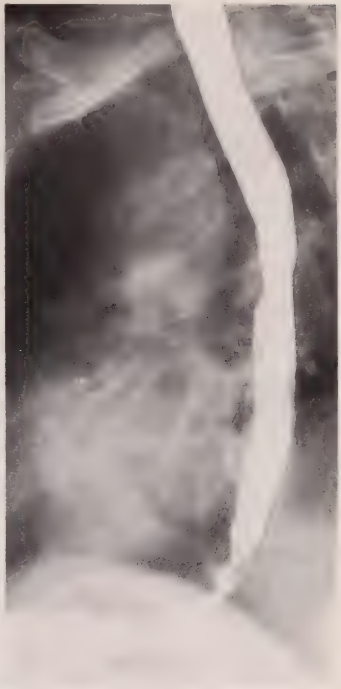

Fig. 4. Upper-GI series repeated one year after completion of radiotherapy and chemotherapy, showing total disappearance of lesion in mid-esophagus.

In our case, however, the initial clue to the diagnosis lay neither in the x-ray nor in the endoscopy, which both seemed to indicate carcinoma, but rather in the clinical history, which pointed in a different direction. The patient's "asthma" probably reflected recurrent episodes of pulmonary aspiration due to partial esophageal obstruction. The prolonged course, the absence of cachexia, and above all the consistent responsiveness of the dysphagia to prednisone all suggested either lymphoma or some benign inflammatory process. Deep biopsy via rigid esophagoscopy revealed the infiltrating histiocytic lymphoma. The patient has had an excellent response to radiotherapy and chemotherapy in what appears to be a most unusual case of primary esophageal lymphoma without extraesophageal involvement.

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The Value of the Barium-Swallow Technique in the Evaluation of the Hypopharynx

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Abstract

To date, detailed radiographic evaluation of the hypopharynx, or laryngeal pharynx, has been by laryngography; appreciation of the information obtainable by the barium-swallow technique has been inadequate. With barium swallow, maneuvers heretofore reserved for laryngography can be easily used to document the presence of mass lesions or areas of fixation in patients with symptoms of dysphagia or odynophagia, or in those with more distal esophageal tumors who are at increased risk in having synchronous head and neck lesions. We illustrate evaluation of the hypopharynx, both in its normal state and in the presence of pathology, using the air-contrast barium-swallow examination, coupled with laryngographic methods.

Routine esophagram has inspired numerous articles on using the double-contrast technique for evaluating the esophagus, especially the thoracic esophagus, for the presence of early carcinoma (1–8). Because of the difficulties encountered in proper timing of exposures and because of the solid barium column present at the exact moment of swallowing, accurate mucosal detail in the area of the hypopharynx is only achieved when specific attention is given to double-contrast evaluation of this region (9).

Usually, the more detailed evaluation of the hypopharynx, or laryngeal pharynx, is left to the laryngogram, as a separate examination, or to direct visualization by laryngoscopy. Two problems arise with this approach. First, tumors of this area, depending on location, may be present with few or no symptoms. Second, the known incidence (1.2%) of synchronous esophageal and head and neck tumors (10, 11) suggests that all areas should be carefully scrutinized when the esophagram is performed.

Methods. A detailed anatomic and functional examination can be easily performed. The patient, while in an erect position, washes down gas-releasing powders, such as EZ Gas, with a sufficient amount of water; one need not observe the strict limit of 10–15 cc used for upper-gastrointestinal (GI) examination. This is then followed by rapid swallowing of high-density barium. EZ-HD barium, 250% w/v is recommended because of its excellent coating properties.

After the cervical and thoracic esophagus have been filmed, the patient swallows an amount of barium sufficient to achieve a good coating of the hypopharynx (12). Given this coating, one can observe the hypopharynx fluoroscopically and record on film its various anatomic structures while specific maneuvers are performed by the patient.

These maneuvers are those generally done during laryngography (9, 13–18) and are useful in defining morphologic and functional changes of the various structures, and so also in determining normalcy, mass effect, or fixation by disease (16).

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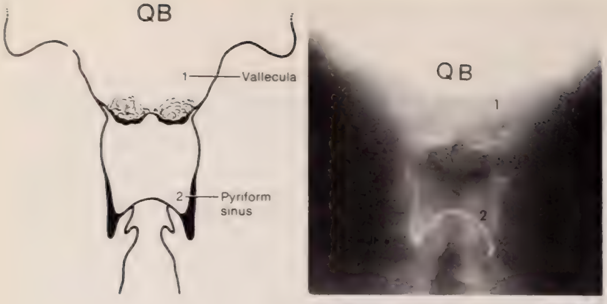
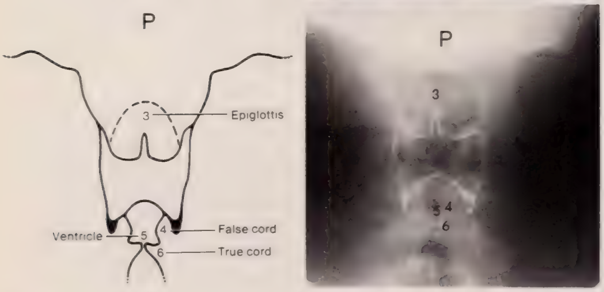
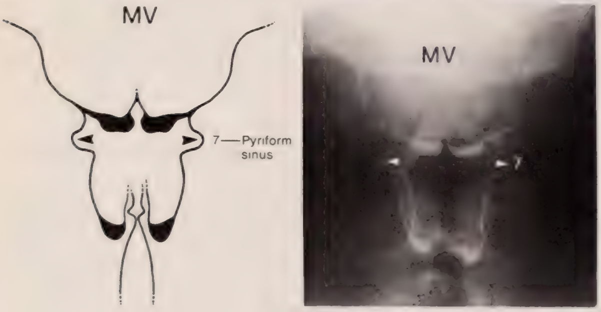

QB
1—Vallecula
2—Pyriform sinus
QB
1
2

Fig. 1. Normal examination of the hypopharynx, diagrammatic and radiographic examples.

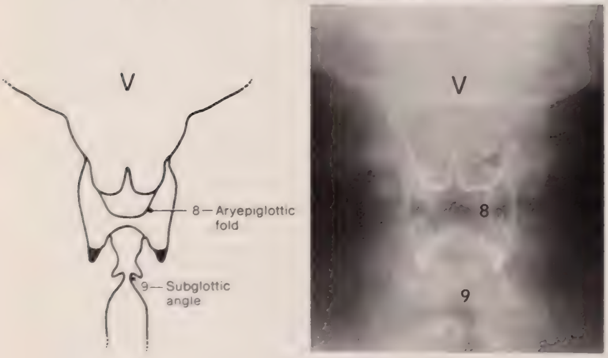
Quiet breathing (QB) effects separation or abduction of vocal cords. Look for the uniform and symmetric mobility of cords.


P
3—Epiglottis
Ventricle—5
4—False cord
6—True cord
P
3
5 4
6

Phonation (P) allows cords to come together toward midline.


MV
7—Pyriform sinus
MV
7

Modified Valsalva (MV), created by forceful blowing against cheeks with lips closed, causes distention of lateral walls and apices of pyriform sinuses. Symmetric distensibility should be observed.


V
8—Aryepiglottic fold
9—Subglottic angle
V
8
9

True Valsalva (V), created by straining down against closed glottis. Laryngeal ventricle and pyriform sinuses contract with adduction of vocal cords. Subglottic angles are nearly at right angles to one another.

For filming in the anteroposterior direction, the patient, in the erect position, should perform the following maneuvers (9, 19); see Fig. 1.

- inspiration or quiet breathing
- phonation
- modified Valsalva
- true Valsalva

Spot filming of each maneuver can be done using either the 105 mm camera or cassette (the latter coned down appropriately).

Discussion. The hypopharynx connects the oropharynx above with the cervical esophagus below. The epiglottis, an arcuate structure, is anterior and superior in the hypopharynx and is bounded on each side by the valleculae epiglottica, which extend to the dorsal aspect of the tongue. These are normally nodular in appearance due to the presence of lingual tonsillar tissues (Figs. 1A, B). The aryepiglottic folds extend inferiorly from the epiglottis to the arytenoids, bounded laterally by the pyriform sinuses. The pyriform sinuses have pointed inferior recesses, or apices, which form the lateral boundaries of the centrally located, diamond-shaped laryngeal ventricle. Impressing on either side of the ventricle superiorly are the false vocal cords. The true cords are sited inferior to the ventricle and demarcate the glottis. All subglottic structures are therefore by definition below the level of the true cords within the trachea. The hypopharynx merges into the esophagus posteriorly at the esophageal inlet, which lies at the level of the sixth cervical vertebral body (12, 19).

During the barium-swallow examination of the hypopharynx, only the supraglottic structures (with the exception of the vocal cords) are normally coated, unless aspiration occurs. However, the air-filled laryngeal ventricle and the false and true vocal cords can be routinely identified and observed fluoroscopically.

The various maneuvers described earlier allow routine visualization of these normal anatomic structures.

Three abnormalities should be looked for: mass effect, mucosal irregularity, and poor distensibility or fixation (16). The most common pathologic cause of these abnormalities is neoplasia (9, 20, 21).

Pyriform sinus tumors are extremely aggressive, exhibiting rapid growth and early spread to adjacent structures (nodes, cords, aryepiglottic fold, subglottic space). When occurring in the lateral wall of the sinus, the tumors are usually exophytic soft tissue masses (Fig. 2); in the apices, they are more infiltrative and are best identified by limited distensibility.

Epiglottic tumors are also aggressive and can exhibit either an exophytic or infiltrative appearance, although the former is more common and more easily identified radiographically. Spread is usually anterior into the valleculae and base of the tongue, occasionally posterior into the posterior pharyngeal wall (Figs. 3A, B).

Aryepiglottic-fold tumors are again either well-circumscribed lesions or infiltrative, spreading into the epiglottis or pyriform sinus (Fig. 4).

True- and false-cord tumors: most commonly

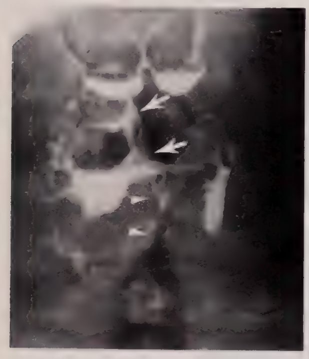
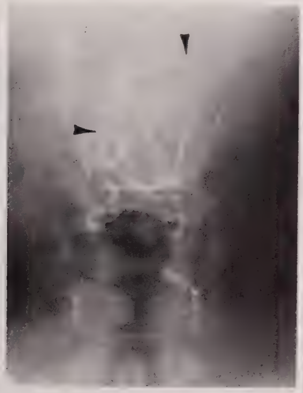


Fig. 2. Left Carcinoma of the right pyriform sinus (arrows). Bulky tumor has invaded right false and true vocal cords as noted by their persistent midline position (arrowheads).



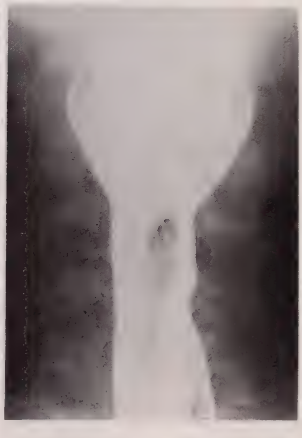
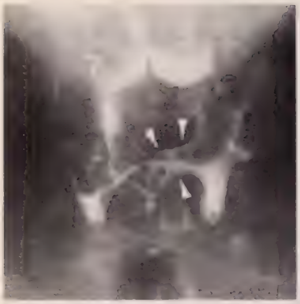
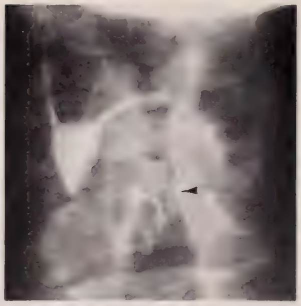


Fig. 3. Center Carcinoma of the epiglottis demonstrated during quiet breathing (arrowheads). **Right** swallowing solid bolus of barium during filming of hypopharynx—epiglottic lesion is obscured.





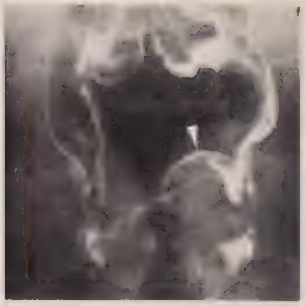


Fig. 4. Left Early carcinoma of left aryepiglottic fold (arrowheads) demonstrated by asymmetry in contour when compared to normal right side.

Fig. 5. Center Infiltrative carcinoma of left false and true vocal cords. Cords retained midline position during quiet breathing and phonation. Flattening of left subglottic angle (arrowhead) indicates subglottic extension of tumor.

Fig. 6. Right Benign polyp of left pyriform sinus (arrowhead). At fluoroscopy, lesion was mobile and did not affect distensibility of pyriform sinus during modified Valsalva maneuver.

identified during fluoroscopy are the infiltrative lesions which exhibit no mass effect but are manifested by fixation or paralysis of one or more of the vocal cords. Bulky tumors are less common but also tend to limit cord mobility by size alone. (Remember, when examining the cords, that complete paralysis is not always present, especially with very early lesions, and that paresis or impaired motion may be the only clue to pathology. This impaired condition is most difficult to identify during the barium swallow and is more readily identified during laryngography.) Widening or asymmetry of the subglottic angle is also a clue to the presence of pathology in the true cord only. Again, evaluation of this angle is more easily achieved at laryngography (Fig. 5).

Paralysis of the cords does not always denote the presence of malignancy. Denervation of the recurrent laryngeal or superior laryngeal nerves by any process, including iatrogenic processes, should be considered. Edema and granulomatous disease (specifically, tuberculosis) can also para-

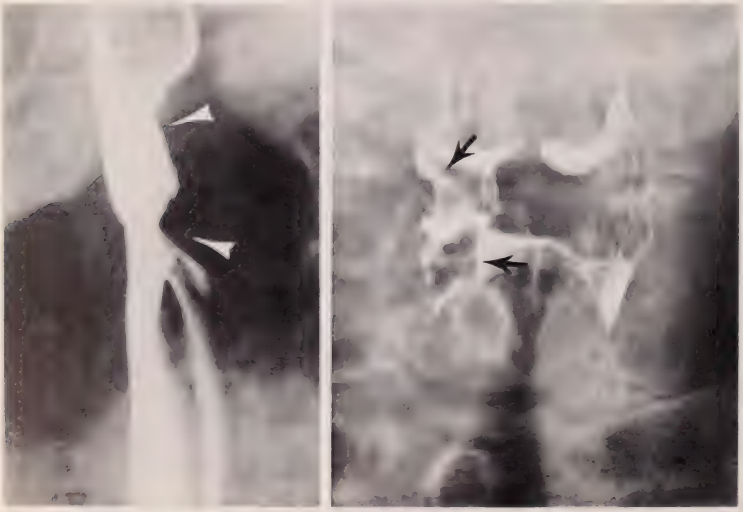


Fig. 7. Patient with ulcerating carcinoma of midesophagus (arrowheads). Film of same patient's hypopharynx revealed synchronous carcinoma of right pyriform sinus (arrows).

lyze the cords. Benign polyps with or without stalks (Fig. 6) and leukoplakia may display mass effect but do not affect cord motility.

Summary. The diagnosis of hypopharyngeal pathology by deliberate and exacting maneuvers normally reserved for laryngography can be achieved easily during the routine barium swallow. The indications for such detailed examinations would include frank symptoms (dysphagia, odynophagia) or the presence of neoplasia distally within the esophagus (Figs. 7A, B). Demonstration of normal distensibility and motility with mucosal preservation and absence of mass effect insures normalcy. Any evidence for fixation, mucosal irregularity, or mass effect can establish a diagnosis of previously unsuspected neoplasia.

A solid bolus of barium in this area during swallowing is not sufficient to determine normalcy. As the final step in the evaluation of the esophagus, a double-contrast examination is important to establish not only morphologic but also functional abnormalities.

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Colon

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Single-Contrast or Double-Contrast Barium Enema: A Historical and Philosophical Perspective

JACK R. DREYFUSS, M.D., AND MURRAY L. JANOWER, M.D.

> The method of roentgen detection of small polypoid lesions of the colon varies. Some radiologists utilize high kilovoltage, multiple compression spot films, with careful fluoroscopy. Others depend on air contrast studies using high density barium. The most important features in the performance of the barium enema examination are a clean colon, high quality roentgenograms, and the skill of the examiner.
>
> Richard H. Marshak, 1980

Historical Review. The use of air to visualize the interior of the colon goes back to the earliest days of radiology. Francis H. Williams of Boston, in his pioneering textbook of 1901 (1), described the injection of air into the large bowel, the prime purpose at that time being to localize its position. However, until the early 1920s, the standard examination of the colon used an opaque contrast material, usually barium sulphate (2). It was generally recognized that small polyps of the colon might easily be missed by this technique.

In 1923, A. W. Fischer of Frankfurt, Germany, began writing articles proposing a new technique of examining the colon using both barium and air, which he called a "combination method" (3, 4). It should be noted that Fischer was a surgeon!

Enthusiastic about what he had seen on a visit to Frankfurt in 1928, B. R. Kirklin returned to the Mayo Clinic and excited the interest of his colleague Harry M. Weber. Challenged by the opportunity to see through overlapping loops, to find small tumors and further evaluate areas of stenosis, Weber modified and perfected the double-contrast examination and was responsible for popularizing its use in this country. Weber's method was done as a single procedure, though at times he found it necessary to have the patient evacuate the enema before air insufflation. He stressed the importance of bowel preparation and preferred his barium to have the consistency of heavy cream. In his 1931 article in the *American Journal of Roentgenology,* Weber noted, however, that he had little success in finding polypoid lesions under 1 cm in size (5).

Stevenson in Texas (6) and Welin in Malmo, Sweden (7), further defined and standardized the double-contrast examination. Welin's method was based on a most meticulous cleansing of the colon, a thin coating of barium on the mucosal surface, and maximum air distention. He claimed that his technique brought the detection of polyps of the colon into the range achieved by study of surgical and autopsy specimens (8, 9). Welin's extensive experience and the correlation of his results still rank as the most impressive in the world literature.

In more recent times, Miller (10) and Laufer (11) have still further advanced the technical perfection and diagnostic accuracy of the double-contrast examination of the colon as a one-stage, primary air-contrast procedure.

Despite these advances, a controversy arose in the last decade among diagnostic radiologists over whether the single-contrast or the primary double-contrast examination was the best procedure for general use. There were also advocates of the more conventional full column barium enema followed by evacuation and an immediate

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air study (12), a type of examination done by many radiologists for years, though not on every patient. The flurry of dogmatic papers and letters to the editor (13, 14) were incredulously received by experienced radiologists, especially those who had long used a combination of the two techniques in their practice. The controversy continues to this day.

Single Contrast & Double Contrast. There is a certain irony in the fact that, in the 1930s, the Mayo Clinic was the leading proponent of the double contrast enema (DCE), whereas 50 years later, it now champions the single contrast enema (SCE). Carlson and his colleagues at the Mayo Clinic have perfected combined SCE and proctoscopy to the point where they claim an accuracy which matches the Welin statistics in colonic polyp detection (15). It should be noted, however, that their SCE is not a casual procedure, but rather one which stresses constant fluoroscopy and vigorous manual palpation of the entire colon during filling. Overhead films have a minor role in this type of study, and spot films are used only to document abnormalities seen at fluoroscopy. Their stated detection rate for polyps of three centimeters or less is 14% and their false-negative rate 6%. This compares favorably with Welin's DCE incidence of demonstrated polyps of 12.5% and Ott's DCE false-negative rate of 8.4% in his recent series (16).

Unfortunately, there are few published reports on the polyp-finding success of the SCE as an independent procedure without proctoscopy. And yet if the truth could be documented, it probably is still the most widely used enema examination, especially in non-academic centers. Such reports as there are tend to be old ones (17, 18), dating back to the 1950's, though still quoted (15) and used to deprecate the SCE when comparing it to the more modern DCE done with meticulous bowel preparation, improved barium mixtures and x-ray equipment, and with a more conscientious approach to the technical perfection of the examination and its interpretation.

Richard Marshak was a colorful, vocal, and enthusiastic proponent of the SCE in the search for colonic polyps. In 1977 (14), he stated, "I prefer the conventional full column barium enema study with compression spot films, high KV [kilovoltage], followed by evacuation and air studies at the same time." He believed that in his hands this combined study was superior to the primary air contrast study alone. And it probably was. Marshak was a master radiologist and a superb fluoroscopist. His extensive experience and his exquisite attention to detail undoubtedly made his studies so rewarding. There are today in this country many other radiologists who have developed and mastered their own techniques for worthwhile SCE and air examinations. As Marshak also said, in 1980, "The most important features in the performance of the barium enema examination are a clean colon, high quality roentgenograms, and the skill of the examiner "(19).

Despite all the controversy, the DCE has gradually gained in popularity since the early work of Welin and the more recent efforts of Miller and Laufer. Whereas Welin's method never achieved wide acceptance in this country, the technical perfection of the examination, as defined by Miller, and the guidelines for interpretation of the DCE, as advocated by Laufer, have made this study available to all radiologists. That it has not yet achieved the encomium of being the standard form of barium enema is due to a number of reasons. There is still doubt as to the value of finding very small polyps. The additional time, films, and radiation exposure are of concern to some radiologists. Others still believe that their own combination method of colon study, developed through many years of experience, is more successful in their hands. And, there are certain patients for whom a DCE would be either unnecessary for a stated clinical question, or would pose an undue risk.

One thing that has been lacking in the literature has been a comparison study of the cancer-finding sensitivity of the SCE and the DCE performed in the same institution. Johnson, Carlson, and associates (20) have recently met that need in a report from the Mayo Clinic. They conclude that the specialized form of SCE done in their clinic was as successful as the modern style DCE in detecting colon cancer above the proctoscopic level. Neither study was found to be superior in finding small lesions or early-stage lesions. As might be expected, experience and proper technique were the absolute prerequisites for good results by either technique.

While this article is more concerned with the detection of benign and malignant colon tumors, the value of the DCE in evaluating inflammatory bowel disease must be mentioned. Although magnificent demonstration of the earliest colonic changes in ulcerative colitis and Crohn's disease can be achieved by the DCE, they may also be documented by a carefully performed SCE in the hands of an experienced examiner. With regard to aphthous ulcers, once thought to be nearly specific for Crohn's disease, they have now been described as also occurring in a number of other inflammatory and ischemic diseases (21). The ability of the DCE to distinguish the earliest change of colitis from the normal and the possible risk of the cumulative higher radiation dose from repeated examinations required of patients with known colitis are still unanswered questions. Time will tell if the current enthusiasm for the use of the DCE in patients with inflammatory bowel disease is justified.

Some Fallacies and Some Truths. The truly artistic and esthetically pleasing appearance of the films from a well done DCE has greatly reassured radiologists and admiring clinicians that the interior of the colon has been beautifully demonstrated and that lesions as small as a few millimeters in size have been documented. With the discovery (and subsequent colonoscopic removal) of so many more smaller polyps than is possible by SCE, the hope has been that the mortality statistics of colon carcinoma would be reduced. Such has not been the case. Even with the gradually increasing use of the DCE during the past two decades, the five-year survival rate has not changed significantly since 1960. This means that the enhanced possibility of finding "small" polypoid cancers, some of which may be "early" and may not yet have metastasized, has not influenced the death rate (3). There is, of course, an explanation. Most carcinomas of the colon are one centimeter in size, or even larger, when they become symptomatic and are found. Studies have shown that properly performed SCEs and DCEs are about equally accurate in finding larger lesions. There is, however, a distinct advantage in employing the DCE to detect polypoid tumors under one centimeter, especially in the several millimeter range (22). The significance of all this is, as Morson has shown (23), that the incidence of invasive carcinoma in polyps over 2 cm is 46%, whereas it is only 10% in polyps of 1–2 cm, and less than 1% when the polyp is under 1 cm. With regard to lesions in the size range under 5 mm, essentially all are hyperplastic mammillations of no present or future clinical importance (24). Therefore, the finding of these tiny polyps on a DCE has not resulted in the earlier detection of carcinoma of the colon (3).

A frequently heard criticism of the DCE is that some tumors do not seem to coat well and have been missed, only to be found at subsequent colonoscopy or surgery. In addition, some lesions have not been detected on DCE, even when their presence was known from a prior SCE or colonoscopy. This has been most disconcerting and has happened to every radiologist who has done a large number of DCE examinations. Kelvin and associates have studied this problem (25) with regard to colorectal carcinoma and concluded that both technical and perceptive errors may contribute to a missed diagnosis. A wholly different approach to performing and interpreting the more complex DCE examination is necessary (26) and failure to be aware of these concepts will significantly diminish the diagnostic accuracy of the DCE.

It is sad but true that the art of colon fluoroscopy is rapidly being lost. Few young radiologists today have been taught how to follow the head of the barium column, to "walk the colon" with a small Berg-type compression cone, or to use ballottement and palpation to evaluate wall pliability and inconstant or constant intraluminal filling defects (3). The skill and experience of the examiner is every bit as important here when doing a SCE as it is interpreting the complex pattern of overlapping lines and gradations in density of a DCE.

Some Common Sense. In any prolonged controversy, there is often more heat than light in the storm of publications generated. Such has been the case in the major controversy over the relative merits of the DCE and SCE in evaluating patients with possible colon lesions. Several years ago, it even went so far that statements were made in our literature suggesting that radiologists who did not use the DCE might be found guilty of malpractice. Nonsense.

When done as it should be, with insistence on total excellence, the SCE in conjunction with proctoscopy has given as accurate results as the DCE in identifying colon polyps and cancers over 1 cm in size. There can be no doubt that the DCE is far superior to the SCE in detecting lesions under 1 cm. But to what advantage? These lesions have an incidence of malignancy of under 1%, and for lesions under 5 mm, the incidence is essentially zero. The finding of these small lesions has not resulted in finding "smaller and earlier" cancers and has, therefore, not contributed to a lowering of the mortality rate from colon carcinoma.

Just as it is all-important to master the techniques of SCE for optimum results, so it is essential to know how to approach the more difficult interpretation of films from a DCE. It is not enough to produce technically beautiful films and then miss lesions of considerable size which are obscured by overlapping lines and differences in adjacent air and barium densities. The present interpretive expertise of many radiologists falls far short of the accuracy recorded in the literature by the masters of the DCE technique.

Given a patient who has been properly prepared for the examination and an examiner who has a conscientious approach to the performance and interpretation of the study, the results in the important size range of colonic tumors may be equal regardless of which type of examination is done (27).

We feel strongly that radiologists should become proficient in both the SCE and the DCE. Each has some specific indications. The SCE is the examination of choice in the young patient, under 35. It should also be used in all so-called "emergency" studies, particularly when the possibility of obstruction or localized perforation (including diverticulitis) is under consideration. Frequently, these studies are done on a less than well-prepared colon or even an unprepared one. A more complex study is not warranted. The SCE should also be used for all elderly, debilitated, or very ill patients and on those who cannot cooperate to perform the more vigorous body movements required for the DCE.

A most meticulous SCE with proctoscopy or the DCE should be done on all patients who have guaiac-positive stools or gross GI tract bleeding. Either one should also be done on patients with a past personal or family history of polyps or colon cancer, and on those with unexplained anemia or weight loss.

In the end, one must come back to the preparation of the patient, the choice of an appropriate technique, and the skill of the examiner. Experience, judgment, and dedication are essential to the successful performance of any diagnostic procedure. Certainly they are the prerequisites for a safe and rewarding evaluation of the colon.

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Post-Ischemic Bowel Obstruction in the Low-Birth-Weight Infant

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It is a rare privilege to contribute to this collection of articles in memory of Richard H. Marshak, M.D. An opportunity to honor him stirs one's ambition to produce something of Nobel Prize quality. Regretfully, my contribution does not meet this ambition, but the subject does pertain to the alimentary tract—and Dick Marshak was internationally known for his studies in this area. I hope that this effort would have been of interest to him.

Today's methods for maintaining life in the very low-birth-weight infant (life support systems, constant monitoring of blood gases, temperature, etc.) have successfully saved the lives of many infants but have resulted in a variety of morbidity problems. These complications include blindness, deafness, intracranial hemorrhage with resulting hydrocephalus and brain damage, chronic lung disease in the form of bronchopulmonary dysplasia, fragile skeletal structures with resulting fractures, and ischemic bowel disease (1).

Ischemic bowel disease (necrotizing enterocolitis) is a common complication of prematurity, characterized by the infant's failure to gain weight, lethargy, unwillingness to feed, temperature instability, and diarrhea that frequently contains blood. This complication varies depending upon the degree of immaturity of the infant and usually has its onset during the first ten days of life. Although necrotizing enterocolitis used to be essentially fatal, today's survival rate in most large intensive care nurseries is now approximately 75%–80%. Consequently, with recovery, the reparative process may lead to cicatricial changes of the bowel, with resulting obstruction usually occurring 11 to 72 days after the onset of the ischemic insult, with a mean interval of 33 days (2).

Stenotic changes with resulting obstruction vary considerably in reported cases and range from 3% to 45% (3). During the past six years we have seen approximately 40 infants who, following recovery of the ischemic damage to their bowel, have developed intestinal obstruction. Approximately 50% of these obstructions have been at multiple sites, and the majority involved the colon.

The general surgeon may be unaware of this complication and consider the obstruction due to more common causes, such as volvulus, peritoneal bands, or Hirschsprung's disease.

The radiographic findings in pending and actual ischemic bowel disease consist of alterations of the normal intestinal gas pattern in the young infant age group. Instead of the normal honeycombed distribution, there is a deficiency of intestinal gas and, less commonly, an increase in the amount of intestinal gas. These signs by themselves are not diagnostic but are suggestive when correlated with clinical findings. The identification of pneumatosis intestinalis, gas in the portal system or biliary tree, and pneumoperitoneum are more pathognomonic diagnostic findings. If there is evidence of perforation, surgical intervention and repair of the perforation is imperative.

Following recovery, which usually occurs over a period of 10 to 14 days, those infants who will develop stenotic areas usually continue to have feeding problems. The onset of abdominal distension and vomiting following this recovery period

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should alert the clinician, surgeon, and radiologist to the complication of bowel stenosis.

Barium-enema or metrizamide studies accurately determine the site of obstruction and the number of stenotic lesions, as well as the length of the strictures. The most common locations are in the transverse and descending portions of the colon, the rectum and distal sigmoid rarely being involved. The radiologic evaluation of small-bowel strictures, which are less common, is more difficult. The identification of distended small bowel proximal to a normal ascending colon suggests additional stenotic areas, probably in the terminal ileum. Attempts to identify these lesions by radiologic studies are usually unnecessary because of the necessity for laparotomy and repair of the colonic strictures, at which time evaluation of the small bowel can be done.

The choice of surgical therapy includes primary resection of the stenotic areas and primary anastomosis or diverting enterostomy followed later by a staged resection and anastomosis. The latter form of treatment is preferred by most surgeons and seems to have fewer complications.

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The Widened Retrorectal Space: Some Radiographic-Clinical Considerations

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Abstract

We discuss and illustrate some causes of a widened retrorectal space. We emphasize that the sign is nonspecific and can be a normal finding. Obese or large patients without rectal disease, as well as a few elderly patients, may also have an enlarged retrorectal space in the absence of disease. However, the sign is of value in the presence of (a) definitive, localized rectal disease, (b) specific diagnostic changes elsewhere in the colon, or (c) clinical and historical correlation.

The retrorectal space has been of interest to radiologists for several decades. Although the importance of a routine lateral rectal film during a barium enema has been questioned (1), the evaluation of the retrorectal space (2 – 6) necessitates this projection. The retrorectal space is best measured from the posterior wall of the opacified rectum to the anterior bony margin of the sacrum at the level of the third through fifth sacral segments (6). No correction is made for magnification.

A classic paper (3) determined that a space of 0.5 cm was found in 95% of normal adult individuals and varied between 0.1 and 0.5 cms. in children (4). These authors considered measurements greater than 1 cm to be abnormal.

In another study, Kattan and King (5) showed that a normal space did not exceed 1.5 cm in patients less than 45 years of age. Above 45 years of age, most normal patients did not exceed this measurement. However, a few had measurements in excess of 1.5 cm and 2.0 cm without apparent cause. Kattan and King believed that age alone can be a factor in presacral (retrorectal) measurements. Body weight and habitus were not considered in their study.

Other authors (2) believe that 2 cm or larger is abnormal. Teplick et al (6) demonstrated widening of the retrorectal space (greater than 1.5 cm) as a normal variant without pathology in 38.4% of 99 adult patients examined. They concluded that a normal variant was the most common cause of the widened space in their series. Of the normal variant group, 73.7% were obese or large patients and 26.3% were of normal body habitus. In the same series, pathologic conditions producing widening of the space were divided into inflammatory (26.3%), neoplastic (23.2%), and miscellaneous (12.1%).

In the consideration of the enlarged retrorectal space, the lateral projection is always evaluated as part of the entire barium enema examination using either single or double contrast technique. No diagnosis is considered to be established by the single nonspecific finding of a widened retrorectal space. However, in the context of other specific radiological findings, as well as the clinical context, the widened space measurement has importance.

The following outline, adapted from Teplick et

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al (6), has helped us to evaluate increases in the retrorectal space.

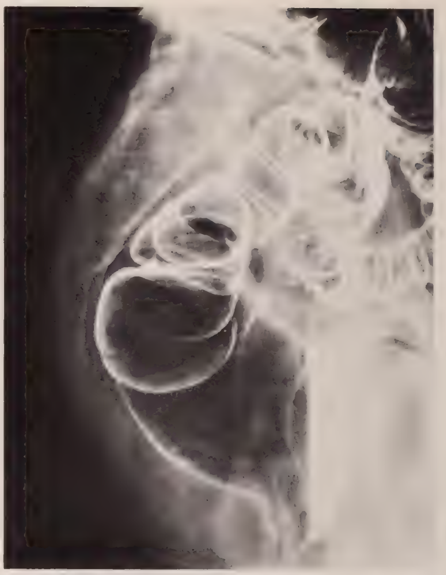
I. Normal Variant
II. Intrinsic Rectal Disease
A. Inflammatory
Ulcerative colitis
Granulomatous processes
a. Crohn disease
b. Tuberculosis
c. Lymphogranuloma venereum
d. Parasitic disease (schistosomiasis)
Ischemia
B. Neoplastic
Carcinoma
Lymphoma
Metastatic disease to the rectum
C. Miscellaneous
Radiation colitis
Amyloid
Pneumatosis cystoides coli
Postoperative deformity
III. Extrinsic Rectal Disease
A. Inflammatory
Retrorectal abscess/inflammation
B. Neoplastic
Lymphoma
Metastatic disease
Sacral neoplasms
a. Chordoma
b. Neural tumors
c. Chondrosarcoma
d. Sacral metastases
C. Miscellaneous
Pelvic lipomatosis
Hernia

A lateral view of the rectum (Fig. 1) reveals a normal retrorectal space with the posterior wall of the rectum assuming a parallel, arcuate course to the sacrum. In an obese male patient (Fig. 2) a widened retrorectal space in the absence of pathology illustrates a normal variant (2).

Although the widened retrorectal space is nonspecific, specific radiographic findings can occasionally lead to a definite diagnosis. In a febrile patient, a retrorectal inflammatory process with opacification of a retrorectal sinus and associated abscess (6) (Fig. 3) is demonstated as the cause of the widened space.

The clinical association of diarrhea with occasional rectal bleeding in an adult Puerto Rican man having a narrowed rectum and a widened retrorectal space (Fig. 4) suggested a granulomatous process, schistosomiasis (7), as the cause. Another more common inflammatory process involving the rectum is chronic ulcerative colitis (3). In a 58-year-old man with a 12-year history of chronic diarrhea and frequent bleeding episodes, chronic ulcerative colitis was confirmed by radiography (Fig. 5) and biopsy.

The diagnosis of another inflammatory process,



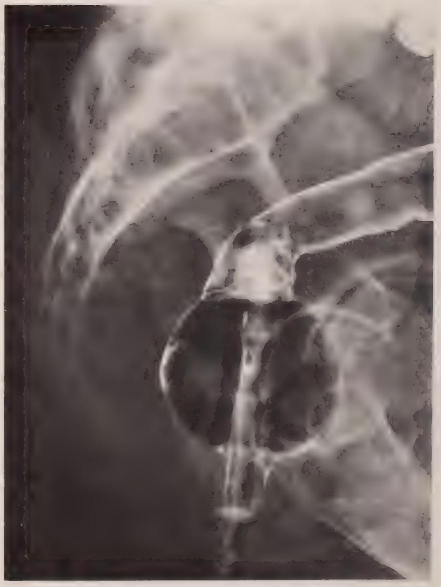


Fig. 1. Top Normal lateral view of rectum; retrorectal space measures 0.5 cm.

Fig. 2. Bottom Lateral view of rectum from double-contrast barium enema examination of obese male patient with no clinical evidence of rectal disease. Retrorectal space measures 3.5 cm.

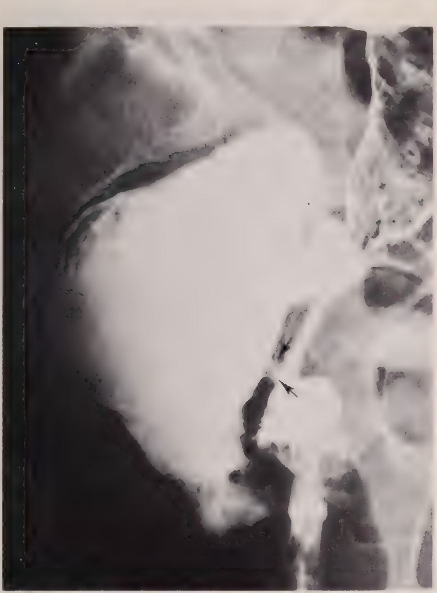


Fig. 3. A widened retrorectal space of 6.5 cm is visualized as a contrast-filled abscess that compresses a narrowed rectum anteriorly; site of communication with posterior wall of compressed rectum is seen (arrows).

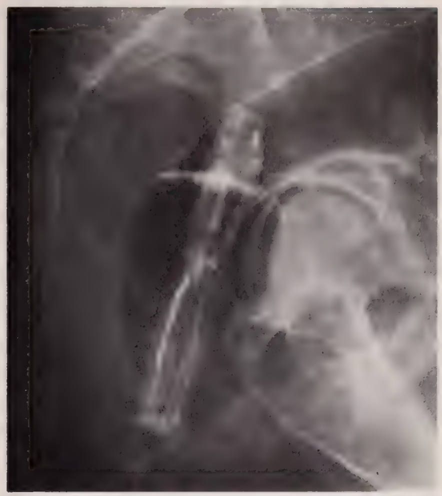


Fig. 5. A slightly ulcerated narrowed rectum and widened retrorectal space of 3.8 cm in patient with chronic ulcerative colitis.

lymphogranuloma venereum (8), in a 42-year-old homosexual man was suggested by a narrowed, tubular rectum and a widened retrorectal space (Fig. 6). Clinical and historical correlation helped to confirm the radiographic impression. For patients with a past history of pelvic disease and subsequent radiotherapy which is recorded, the

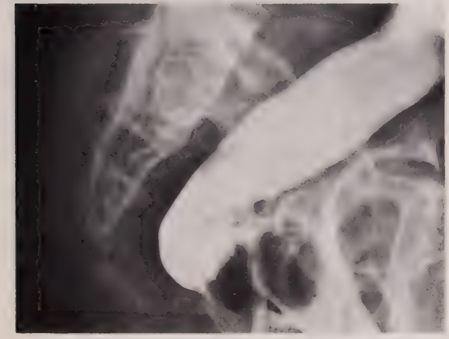


Fig. 4. A retrorectal space of 2.0 cm is measured in lateral projection in patient with schistosomiasis.

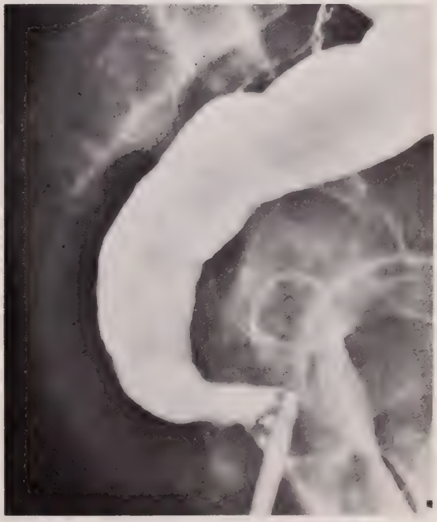


Fig. 6. A single contrast barium enema lateral projection with retrorectal space of 1.7 cm correlated with history of rectal homosexual activity led to final diagnosis of lymphogranuloma venereum. Apart from widened retrorectal space, film is nonspecific.

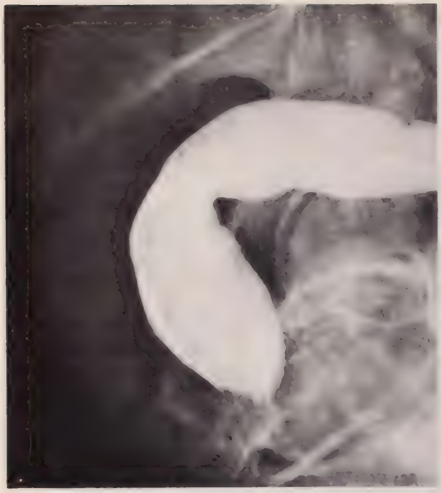


Fig. 7. Lateral single contrast examination of patient with changes of rectum after radiation associated with successful treatment of carcinoma of urinary bladder. Retrorectal space measures 4.5 cm.

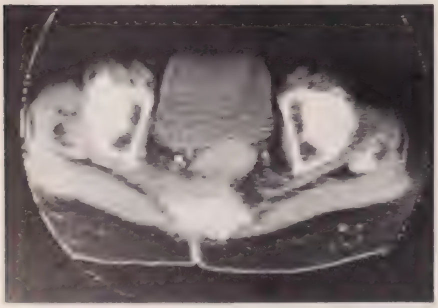
demonstration of a narrowed, somewhat elongated rectum and an enlarged retrorectal space correlates well with radiation injury to the rectum (9) and the sequella of radiation proctitis (Fig. 7).

The visualization of blastic destructive bony changes in the sacrum in association with a widened retrorectal space (Fig. 8) readily leads to the diagnosis of secondary metastatic changes. Similarly, lytic destructive changes in association with a widened retrorectal space and extrinsic pressure on the rectum readily reveals the secondary nature of metastatic process as a cause for the radiographic changes.

Occasionally, metastatic disease to the perirectal area alone can widen the retrorectal space (2). In a patient with prostatic carcinoma and obstipation, a barium enema examination (Fig. 9) revealed a mass invading and widening the retrorectal and perirectal space on computerized tomography. The rectum is also involved posteriorly.

The evaluation of the enlarged retrorectal space in the presence of a lucent soft tissue mass in the pelvis (Fig. 10) and slightly elevated, contracted urinary bladder visualized at excretory urography has identified pelvic lipomatosis (10) as the etiology for the narrowed rectum and the widened retrorectal space (Fig. 10).

Although the previously described, more unusual disease processes are associated with a narrowed rectum and enlarged retrorectal space, pri-



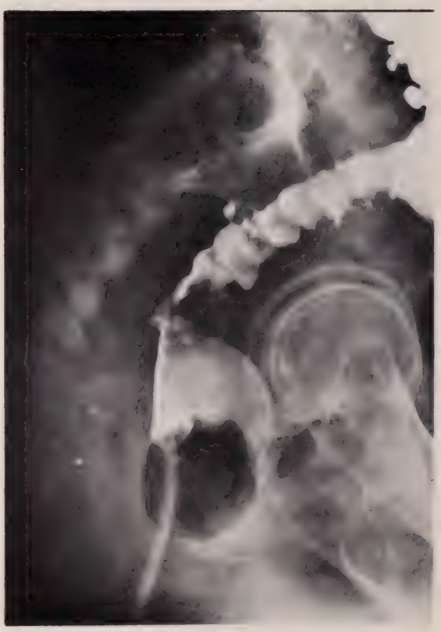


Fig. 8. Computed tomography **(left)** reveals blastic sacral destructive changes and soft tissue mass extending into retrorectal space. Lateral barium enema view of rectum **(right)** with retrorectal space of 2.2 cm shows compression of rectum posteriorly and again reveals blastic metastasis to sacrum. *Courtesy of Mark Goldman, M.D.*

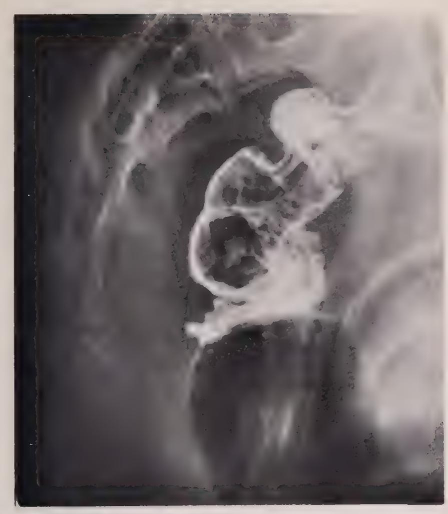


Fig. 9. In lateral view from double contrast barium examination, increase in retrorectal space (2.8 cm) is associated with irregularity of posterior rectal wall in 80-year-old man with prostatic carcinoma.

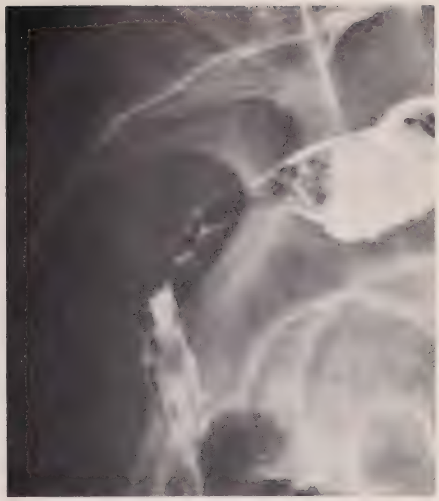


Fig. 11. Narrowed, ulcerated primary carcinoma of rectum with 3.0 cm retrorectal space is observed on lateral double contrast enema examination. Osseous structures are intact.

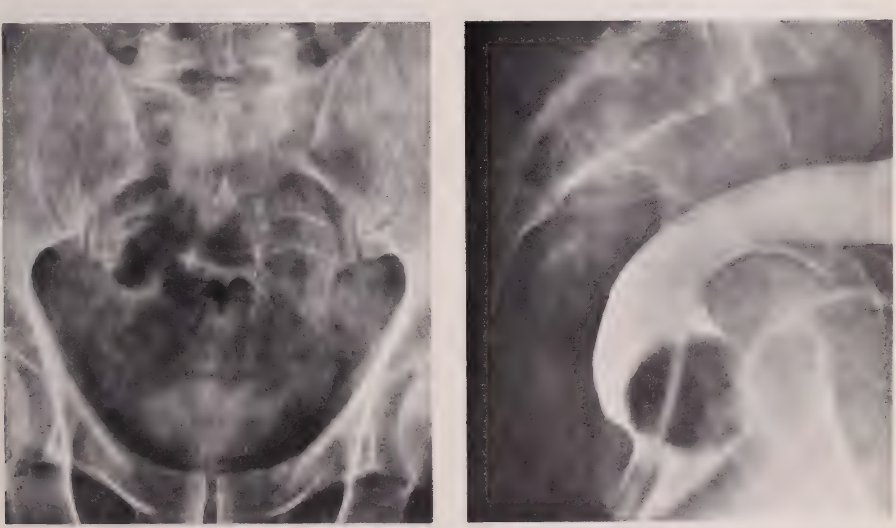


Fig. 10. Left Lucent pelvic tissues on plain film anterior-posterior projection, in association with (**right**) narrowed tubular rectum and increased retrorectal space of 3.9 cm, establishes diagnosis of pelvic lipomatosis.

mary carcinoma of the rectum should always be the first diagnostic consideration (Fig. 11). Specific findings of mass and ulceration of the mucosa helped to identify the process as arising primarily from the rectum. Confirmation by biopsy established the diagnosis.

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Continent Ileostomy

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Abstract

We have performed single-contrast barium, Gastrografin, and double-contrast barium-air studies in selected cases from a series of 300 patients who had undergone total proctocolectomy and construction of a continent ileostomy. The most important complication was dysfunction of the pouch valve, usually deintussusception of the nipple resulting in difficult intubation or incontinence. The commonest form of deintussusception was partial asymmetrical reduction, primarily of the mesenteric aspect of the nipple. Symmetrical reduction and complete extrusion also occurred. We found that radiologic examination provided an accurate assessment of abnormalities which called for surgical revision or medical therapy.

The continent ileostomy, or Kock pouch, is designed to provide the patient with a reservoir that remains completely continent of feces and gas in the intervals between voluntary evacuation. Evacuation is accomplished by inserting a catheter through the stoma. If the pouch holds about 800 cc, it can be emptied twice or three times a day. There is no need to wear a collecting appliance, and such problems as peristomal skin irritation and odors are avoided. Also, the stoma is unobtrusive and is less likely to produce a significant change in the quality of life (1–5). (Table 1)

The major indication for the procedure is proctocolectomy for ulcerative colitis and colonic polyposis in young patients (6). The pouch can be fashioned as a primary procedure at the time of proctocolectomy in patients who are not seriously ill, such as those with the syndrome of toxic megacolon. Secondary conversion of the conventional ileostomy can be performed at a later time.

Fashioning the Ileostomy. The components of a well-constructed continent ileostomy are the ileal reservoir; a valve to prevent leakage of ileal contents; an efferent limb leading from the valve to the stoma; and an afferent limb leading to the pouch (6, 7). All four components are constructed from the terminal 40–45 cm of ileum.

The reservoir is fashioned from approximately 30 cm of the proximal segment by folding the segment into a *U* shape, the outflow tract facing cephalad. The two 15-cm limbs are joined along the antimesenteric borders. The incision is extended 2–3 cm into the afferent limb to facilitate separation of the afferent (inflow) and efferent (outflow) tracts when the reservoir is closed. This separation is required to prevent kinking of the afferent limb when constructing the nipple and to avoid direct flow of enteric contents into the nipple opening.

The nipple valve is made by intussuscepting the efferent ileal loop into the pouch for a distance of 4.0–4.5 cm and anchoring the intussusception in place with sutures. When the valve is smaller than 3 cm in length, it is less effective in producing continence and, if minimal slippage occurs postoperatively, is more likely to lead to incontinence. The intestinal plate (pouch wall) is closed apex to apex. By forming the pouch in this way, the peristaltic activity within the pouch is rendered nonpropulsive. The posterior aspect of the reservoir immediately behind the efferent segment is sutured to the abdominal wall fixing the pouch in place. The entire outflow tract is within the anterior abdominal wall.

By gradually increasing the intervals between evacuation, pouch capacity increases from an initial 75–100 cc to 500–800 cc by the third to sixth postoperative month (Fig. 1).

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TABLE 1
Comparison of Complications of Standard and Continent Ileostomy

	Standard ileostomy	Continent ileostomy
Metabolic changes		
Oliguria, mild systemic acidosis due to obligatory sodium loss (30–40 mEq day)	+	+
Urolithiasis: alteration of sodium potassium in urine (renal conservation of sodium)	+	+
Excessive stomal output, steatorrhea responsive to oral antibiotics: stagnant loop syndrome, increased anaerobic bacteria and bacteroides	−	+ (small series of cases)
Mechanical dysfunction of stoma		
Obstruction	−	+
Nonspecific superficial	+	−
Prestomal ileitis	+	+
Reduction of nipple valve	−	+
Perforation during intubation	+ (highly unlikely)	+ (efferent segment and pouch)
Peristomal disease		
Peristomal excoritation	+	−
Peristomal abscess	+	−
Erosion of stoma with production of fistual	+	−
Peristomal hernia	+	−
Prolapse of stoma	+	+ (nipple)
Unpleasant odors in bag after certain foods	+	−

+ = complication occurs; − = complication does not occur.

On plain film examination, the normal ileal reservoir usually appears as a slightly lobulated, gas-filled structure, fixed in the middle or on the right side of the pelvis. This position is selected for two reasons: The pouch rests on the pelvic floor and will not readily pull away from its attachment to the anterior abdominal wall; and the stoma can be placed just above the pubic hair line. The distended ileal pouch is more or less round to oval and has an intact ileal mucosal pattern. The nipple valve, when projected in profile, protrudes as a soft-tissue density into the pouch perpendicular to the adjacent wall of the reservoir and the abdominal wall at the base of the nipple. A mottled "fecaloid" pattern may be evident depending on the quality and quantity of the pouch contents.

The ileal reservoir can be examined both with orally administered contrast material or by single or double contrast ileal enema. To reduce the volume of ileal contents, it is desirable that the patient fast and the pouch be open to drainage for a few hours prior to the examination. This is particularly true for the retrograde method. In the antegrade study, ingested barium enters the pouch from above during the course of an upper gastrointestinal series and small-bowel follow-through. The afferent limb can almost always be clearly delineated by the antegrade study. In the retrograde study, the pouch is evacuated before the contrast medium, which can be high-density barium, is inserted. Supine, prone, and various oblique positions are utilized to coat the mucosa of the pouch, and spot radiographs are taken to delineate the nipple in profile and *en face* during both types of examinations. Air is added for the double-contrast study, which has the advantage of displaying the internal architecture of the reservoir without the need for compression. Reflux of contrast material into the afferent limb of ileum may or may not occur during the retrograde study.

The two examinations can be combined after barium that has been swallowed reaches the ileal pouch. At this time, the barium from the pouch is evacuated and air introduced, with or without high-density barium. Patients in the immediate postoperative period with symptoms suggesting anastomatic breakdown are examined with Gastrografin after the pouch is drained.

A base line examination of the pouch with emphasis on nipple anatomy is suggested 3–4 months postoperatively, when the pouch is ma-

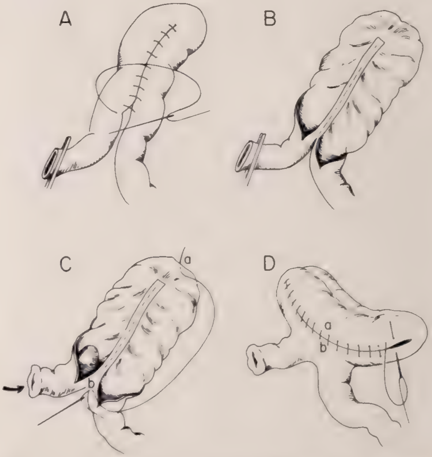

Fig. 1. **A** Suturing of *U* loop of distal ileum. Clamp is on efferent limb and stoma. **B** Opening ileum in preparation for forming actual pouch. **C** Nipple and stoma are fashioned. **D** Apex to base (a to b) suturing of ileum to complete pouch.

ture. The radiological examination may also be used as a method of measuring pouch capacity. Probably the best method for the latter is to allow antegrade filling with barium to tolerance, then drain, checking with roentgenograms for completeness of drainage and measuring the quantity of material removed.

The mature pouch is a large distensible sac with smooth, pliable margins. Contractions that are nonpropulsive and involve part of the pouch wall are evident at intervals. The mucosal architecture of the pouch demonstrates smooth linear folds at right angles to the axis of the nipple (Fig. 2). The surgical closure lines cannot be readily identified. The pouch, on emptying, collapses readily about the nipple and the nipple maintains its position. The afferent loop usually enters the pouch at its inferomedial aspect and lies posterior in the sacral hollow because the anterior wall of the pouch is sutured to the anterior abdominal wall. A segment, 3–4 cm, of distal small bowel may be adherent to the pouch. In reoperated-on pouches, the entry of the afferent limb may be elsewhere in the pouch. The efferent limb or outlet of the pouch is usually not opacified if the nipple valve is continent. Retrograde study of the outlet may be performed by obturating the stoma with the balloon of a Foley cathether and using low-density barium to render the short (5-cm) canal opaque; the lateral or steep right posterior oblique projection should be used.

As the stoma lies in an anteroposterior plane, the nipple, theoretically, should be best and most completely seen in the lateral view. However, in this position, the nipple is frequently obscured by bony structures of the pelvis and by small-bowel loops. Therefore, the nipple is usually evaluated in a 60° right posterior oblique position (Figs. 3, 4). First, a straight line is drawn across the base of the nipple, representing the attachment of the nipple to the pouch wall. The actual line sometimes can be determined if folds can be clearly delineated within the pouch and traced to the nipple base.

The angle that the nipple makes with the line of the base is about 90°. The nipple has the shape of a cone with a truncated tip. The segment inferior to the lumen is invariably smooth and of the same thickness from base to apex. The segment superior to the lumen is thicker, generally, and wider at the base (consisting of two layers of folded mesentery). The contour, here, may be slightly undulating. The length of the nipple, base to apex, should be 3–5 cm. The *en face* appearance of the nipple is that of a round, smooth filling defect. In the prone position, particularly with compression, a clear complete line of barium is seen delineating the circumference of the nipple. The double contour that may be evident along part of the margin is secondary to slight deviation of the nipple axis from the anteroposterior plane of the abdomen (Fig. 5) (8–10).

Radiological Findings: Complications

In our series of 300 patients, no patient had the reservoir removed for development of complications (Table 2). The most common immediate postoperative complication was a fecal fistula. When demonstrated on contrast study, the fistulous tract extended from the pouch inferiorly to the perineum (Fig. 6). Patients with a major fecal

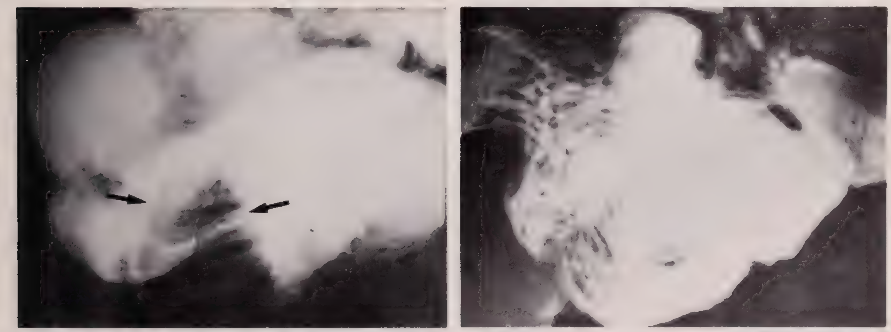

Fig. 2. Left Normal continent ileostomy opacified by barium from above is incompletely filled. Nipple is seen as smooth conical filling defect (arrows). Both margins of nipple form sharp acute angles with adjacent pouch wall. Efferent limb is inferior but not opacified due to nipple continence. Dilation of proximal small bowel due to adhesions resolved with conservative therapy. **Right** Active nonpropulsive, noncircumferential contractions are clearly evident and were seen at fluoroscopy. There is no escape of barium through nipple.

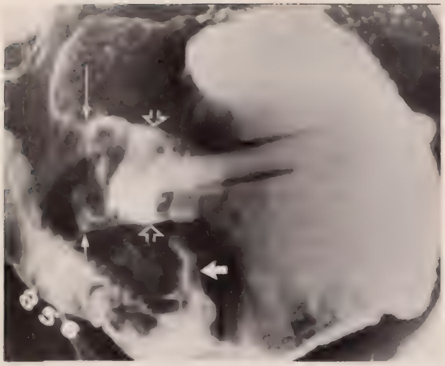

Fig. 3. Above Nipple is normal in length (open arrows). Contour is smooth, shape is conical, and acute angles at base are well maintained (long arrows). Entry of afferent loop slightly distorted by semilunar saclike structure (arrow) created by revision following original surgery. Mucosal pattern is linear: folds are sharp.

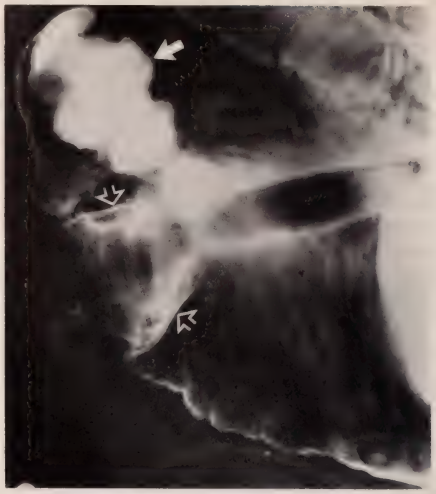

Fig. 4. Right Examination of pouch with barium given by mouth and air instilled in retrograde fashion. Nipple is short but lateral basal angles are well maintained (open arrows); contour is smooth; nipple continent despite lack of usual length; pouch mucosa normal. Segment of ileum in continuity with pouch (arrow) but isolated from revised afferent loop is remnant of initial afferent loop.

fistula for whom conservative therapy failed required temporary loop ileostomy to ensure closure of the fistula.

Delayed complications, such as nipple valve dysfunction, tend to occur in the first 4–5 postoperative months. The most common dysfunction is deintussusception of the nipple valve. This results in difficulty with intubation and, eventually, loss of continence. Deintussusception has been attributed to a number of mechanisms, the major two being peristaltic activity within the nipple and inability to anchor the wall of the nipple firmly in the area of the mesenteric fat and vessels, which are wedged between the intestinal walls of the nipple. With partial loosening of the nipple attachments, usually as a result of one or several sutures pulling out, intubation becomes difficult. This difficulty results from angulation of the lumen due to the resultant change in orientation of the nipple. The tube now encounters

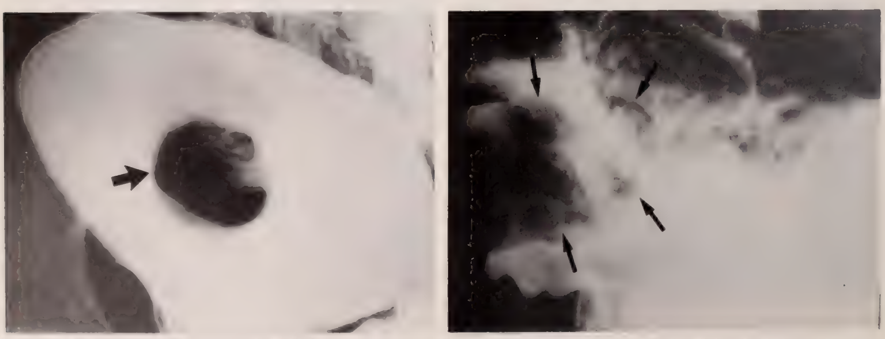

Fig. 5. **Left** Antegrade examination of pouch demonstrates en face appearance of nipple valve. Base of valve outlined by barium is circular in configuration (arrow). Because of slight rotation of normal nipple valve from anteroposterior axis, a “double contour” is evident on one side. **Right** Entire nipple valve is outlined in profile (arrows).

TABLE 2
Complications Following Continent Ileostomy, 300 Cases

	No. (%)	Comments
Early		
Minor fecal fistula	8	All closed rapidly using sump drainage of reservoir
Major fecal fistula	2	Temporary loop ileostomy proximal to reservoir; all leaks closed
Total	10 (3%)	
Early and late		
Small-bowel obstruction	6 (2%)	Surgical lysis of adhesions
Postoperative day 7–12		
Hemorrhage from reservoir:		
Minimal	6	
More profuse at time of expected suture line slough	8	Transfusion and irrigation with levarterenol
Total	14 (5%)	
Late		
Pulmonary embolus	3 (1%)	
Perforated gastric ulcer	1 (0.3%)	Post lysis of adhesions on large doses of steroids

a cul-de-sac formed by one wall of the deintussuscepted nipple rather than the lumen. In more complete deintussusception, the valve may be totally extruded.

These complications are readily demonstrated radiographically:

Asymmetrical partial reduction invariably involves the mesenteric aspect of the nipple and causes shortening or disappearance of the mesenteric wall of the nipple.

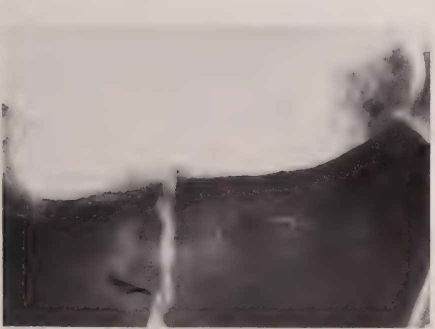

Fig. 6. Fecal fistula. Linear tract of contrast material extends from pouch to perineum. Patient, recently operated on, was 23 years old with 6-year history of ulcerative colitis. Fistula eventually resolved with treatment by diverting-loop ileostomy.

Symmetrical partial reduction results in the nipple being generally shortened with retention of symmetry.

Complete disappearance of the nipple from the pouch in cases of total extrusion produces elongation and tortuousity of the ileal outflow tract. In the profile view of the nipple, increasing angles at the base is a sign of early deintussusception (Fig. 7). In that category, widening of the base, particularly of the mesenteric aspect of the nipple, suggests early loosening of the nipple attachments. Changes in orientation of the nipple enhanced in the collapsed pouch also suggests a similar insult or loosening of the pouch attachments to the anterior abdominal wall. Indeed, in all significantly incontinent valves, there is some loosening of the pouch from the anterior abdominal wall. With further loosening and deintussusception, the nipple actually diminishes in length and eventually extrudes. The efferent segment is readily opacified in this situation especially during the antegrade barium study. In the *en face* view, the normal "circle" of barium which is clearly defined around the nipple is asymmetrical or incomplete.

Fistula is a less common cause of incontinence than reduction of the nipple valve. It occurs between the lumen of the pouch and, usually, the lumen of the outflow tract at the base of the nipple valve. Tracking directly to the anterior abdominal wall has been reported. Incontinence occurs because the valve is bypassed. The most common etiology is ischemic necrosis of a portion

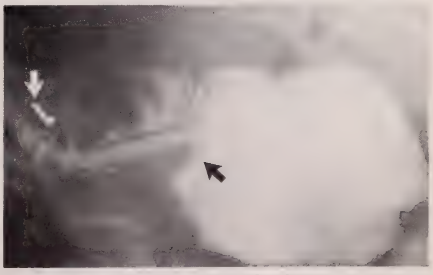

Fig. 7. Two months postoperatively, this 33-year-old man noted difficulty with intubation of pouch, which progressed to incontinence of nipple valve. Intussusception of the nipple is almost totally reduced (black arrows). Acute angle is still maintained inferiorly but superior angle is effaced. Length of nipple is considerably but asymmetrially reduced. This is commonest form of deintussusception. Marker 1 is at the cutaneous stoma (white arrow). Efferent loop, never seen with a continent valve, is identified by barium coating circumferential ileal folds.

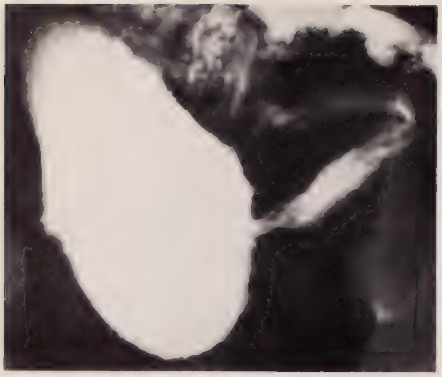

Fig. 8. Recurrent granulomatous enteritis involving distal 8″ of ileum and pouch. Total proctocolectomy and construction of continent ileostomy was performed 2 1/2 years earlier because of presumed ulcerative colitis of 13 years' duration. Afferent limb shows findings typical of Crohn's disease. Biopsy of pouch showed colonic mucosa with severe chronic and acute inflammation but no granulomata.

of the bowel wall constituting the valve secondary to presence of the transfixing sutures. This produces a tract through the nipple which eventually fistulizes, usually to the outflow tract. A water-soluble contrast agent is preferable in demonstrating this relatively narrow abnormal channel, most readily visualized on retrograde examination. Actual prolapse of the nipple through the stoma is another cause of mechanical nipple dysfunction.

Perforation during intubation may occur in the efferent limb. Perforation of the pouch itself can be demonstrated by retrograde Gastrografin study.

Nonspecific ileitis develops in some patients and causes abdominal cramping and diarrhea (3). The inflammatory changes may be confined to the mucosa of the reservoir (pouchitis) or may also involve the adjacent ileum proximal to the pouch. The inflammation usually subsides with antibiotic or azulfidine therapy. Roentgenologically, the ileum shows considerable irritability. The mucosa may appear entirely normal or show evidence of edema and ulcerations. Recurrent Crohn's disease is uncommon, since the operation is not knowingly performed in patients with granulomatous colitis (Fig. 8).

We believe that the major long term postoperative complication, deintussusception of the nipple valve, can be significantly reduced by insisting on frequent intubation and emptying in the early postoperative period.

Discussion

In our series of 300 cases, to date 267 patients (89%) were fully continent and 32 (11%) occasionally wear an appliance, particularly at night. These results compare quite favorably to other series of cases (11–13).

The continent ileostomy has proved a valuable procedure with few significant complications. The radiologic examination is primarily valuable for demonstrating the configuration of the nipple valve in patients with difficult intubation or incontinence. Clear delineation of nipple valve pathology is extremely helpful as a guide to the surgeon where valve revision is required. Fiberoptic endoscopy may also be used for this purpose (14).

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Oral Barium Tracer: An Adjunct for Barium Enema Preparation

RUBEM POCHACZEVSKY, M.D.

Orally administered barium (240 gm; 8 oz) as a tracer can serve as an objective and dependable criterion for accurately evaluating preparation for a barium enema. Orally administered barium persists longer than feces after routine preparation and can therefore be used as an intrinsic indicator of the thoroughness of colonic preparation. Since the residual intracolonic barium tracer remains in a liquid state, it does not interfere with the subsequent barium enema. Fecal residues can be confidently identified by their incorporated barium marker. Due to their semiliquid state, barium-interlaced residues less than 1 cm in diameter tend to "disappear" or dissolve when the barium enema is given. The oral-barium-tracer technique significantly increases and improves the number of successful barium enemas that can be performed. It further aids in the distinction of true polyp from feces.

Several objectives and advantages are realized by supplementing the routine preparation for barium enemas with an oral dose of a special barium sulfate preparation. The use of oral barium as a tracer or marker can help to objectively evaluate patient preparation prior to barium enemas and to expedite the enemas despite less than optimal preparation. It serves as a guide in improving patient preparation. And the barium tracer also aids in the distinction of true polyps from small fecal residues.

Previous attempts to employ oral barium sulfate tracers for evaluating adequacy of colonic preparation were not as effective as the method described here because only small tracer doses (30–60 gm) were administered. For most patients, preliminary films showed a minimal amount of barium remaining in the bowel. If larger amounts of retained barium were noted, inadequate preparation was postulated, the examination was cancelled, and more rigorous preparation instituted. For approximately 20% of patients, cleansing enemas were administered in the fluoroscopy room (4).

A modification of the technique is described here which redesigns and expands the role of barium as an oral tracer for the evaluation of colonic preparedness.

Material and Methods. In addition to routine preparation for barium enemas, patients were given an oral dose of 240 gm (8 oz) of a special high-density, liquid barium sulfate (Liquid Polibar, E-Z-EM Co.). Routine preparation usually consisted of a low-residue diet for two days; hydration, saline cathartics, four 5-mg tablets of bisacodyl the day before the examination, and one bisacodyl rectal suppository on the day of the examination. The 240 gm of oral barium tracer was given one day prior to the barium enema. On the day of the scheduled barium enema, preliminary films of the abdomen were taken and evaluated prior to the initiation of the examination. The double contrast technique was used in most cases. A total of 100 barium enemas was performed.

Results. It was established that the 240 gm of orally administered liquid barium persisted longer than feces after routine colonic preparation (Figs. 1, 2). A study of the amount of barium residue in the colon of 100 patients (not including examinations cancelled because of inadequate preparation) yielded these results:

none	4
minimal	49
moderate	20
considerable	27

Residual colonic barium from the tracer dose was often present in liquid form. Only four patients were entirely free of retained intracolonic barium. Barium enemas showed that these patients were optimally prepared. The liquidity of the residual tracer may have been due in part to

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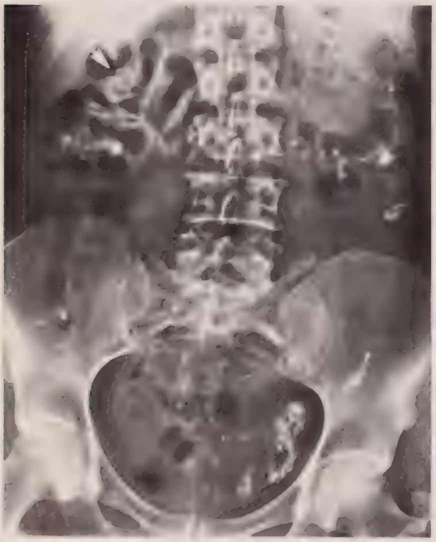
hydration and also to the fact that the particular barium sulfate tracer preparation selected contained a high percentage of sorbitol as well as special suspending agents. The retained barium, however, did not interfere with the subsequent successful double contrast studies.

When fecal material was present, it was clearly identifiable per se or by virtue of its opacification by incorporated barium. This enabled cancellation of inadequately prepared patients.

Discussion. A recent survey (1) of radiological techniques for barium enemas used in leading medical centers throughout the world revealed that preliminary films of the abdomen were taken in slightly more than half of the institutions surveyed. The most important advantages postulated for the preliminary film included foreknowledge with respect to adequacy of preparation; demonstration of contraindications to barium studies; delineation of pathology involving other organ systems; and delineation of densities that could be misinterpreted as extravasated barium had the barium enema preceded the preliminary film (2). Eisenberg and Hedgcock (3), however, noted definite limitations on their ability to judge adequacy of preparation solely on the basis of a routine preliminary film. They indicated that faulty estimates regarding the amount of retained fecal material could lead to unnecessary postponements and more rigorous and inappropriate preparation (Fig. 2). However, with the oral barium-tracer technique, the presence or absence of significant amounts of feces could invariably be objectively and more accurately determined. There were no disagreements between assessments of adequacy of preparation based on preliminary films and what was found during the barium enema itself. Unprepared patients were, as a rule, successfully reprepared. This high degree of accuracy with respect to judging adequacy of preparation was due to the larger amount of oral barium (240 gm) used as a tracer as compared with amounts used in previous studies (4).

An important and probably the most significant concomitant benefit of this tracer technique was the discovery that when moderate amounts of fecal residue were present, as judged on the preliminary film, they tended to "disappear" or dissolve during the course of the barium enema. Barium enema results in 16 cases with barium-



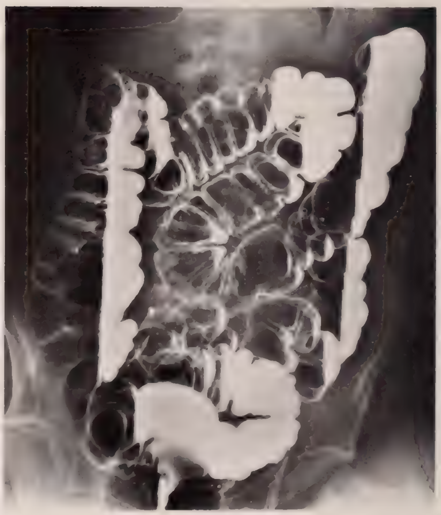


Fig. 1. Left. Preliminary abdomen film. Fecal residue is simulated by colonic haustra and hepatic flexure gas pattern (arrow). However, small amount of barium present indicates adequate preparation.

Fig. 2. Right. Subsequent double-contrast examination of same patient confirms adequate preparation.

impregnated fecal material on preliminary films were as follows:

complete dissolution of residue	6 (37%)
persistent opacified residue (barium incorporated in fecal material)	8 (50%)
persistent nonopacified fecal residue	2 (12.5%)

Dissolution occurred particularly in the case of residues less than 1 cm in diameter. Complete dissolution is presumably related to the semiliquid state of the residues, which therefore either thoroughly mixed with the orally administered barium or had been dispersed by the barium subsequently introduced per rectum. The orally administered barium that remained free and unmixed with fecal residues also dissolved in the rectally introduced barium. Occasional opacified fecal residues were easily distinguished from small polyps. Polyps, as a rule, are surface coated by the barium, which cannot be incorporated within their substance.

Successful barium enemas, free of unidentified filling defects, were achieved in 98 of the 100 patients examined, an almost ideal result. This contrasts with an average success rate of only 85% with patients in our institution who had had identical preparation but had not used the oral tracer.

Because small amounts of barium remained in the cecum in the majority of patients (Figs. 1, 2), it was easier to determine when the cecum was entirely filled during the barium enema proper, particularly when reflux into the terminal ileum or appendix did not occur or was not desirable. With the tracer, the proximal extent of tumors that would cause obstruction to the retrograde flow of barium may also be documented on the preliminary film, and this was valuable preoperative information. Large-bowel obstruction was not found to be a contraindication to tracer use, since the special barium preparation tends to remain liquid for a relatively long period of time. In addition, most patients with complete or partial large-bowel obstruction undergo emergency colostomies or other emergency surgical procedures.

The oral barium-tracer technique is also useful in patients for whom barium enemas are contraindicated or are not feasible due to poor cooperation. Colonic examination can still be performed on these patients by rectal air insufflation, a technique previously described (5)—provided that a sufficient amount of intracolonic liquid barium remains, as it often does.

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Anterior Pararenal-Space Infection from Colon and Appendiceal Perforation

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Abstract

In a retrospective study of 18 patients, I found that the plain abdominal radiograph was most useful in showing anterior pararenal-space infection caused by colonic or appendiceal perforations. In most patients, the abscess appeared as a gas-containing, retrocolic or pericolic mass, which remained fixed on different radiographic projections. Usually, the abscess extended to the properitoneal fat laterally, did not obscure the ipsilateral psoas and kidney outlines, and was accompanied by ileus. Other signs of anterior pararenal-space abscess, such as hepatic or splenic angle obscuration and ipsilateral kidney or duodenum displacement, were infrequent. Spread of gas to the contralateral abdomen occurred in only 2 of 18 patients.

Ultrasonography and computed tomography, employed in four cases, corroborated the diagnosis and more precisely defined the abscess size and location.

For eight patients, studies of the colon were done using contrast-medium enemas, and these provided supportive information by confirming the presence of an extraperitoneal inflammatory mass. The contrast studies showed extravasation, with colon perforation, and lack of appendiceal filling, with appendicitis or colonic mucosal edema adjacent to the abscess.

Perforation of the colon or appendix is the most common cause of anterior pararenal-space infections. In reviewing 84 patients with anterior pararenal-space abscess, Altemeier and Alexander (1) found that colon lesions accounted for 31% of the abscesses, appendix lesions for 18%, pancreas lesions for 14%, duodenum and bile-duct lesions for 9.5%, ileum lesions for 3.5%, and stomach lesions for 3%. Enteric pathogens in the extraperitoneal loose-fibrous and fatty tissue encounter little resistance to spread. Because signs and symptoms of anterior pararenal space infection appear late and are difficult to interpret, retroperitoneal colon and appendiceal perforation can be cryptic clinically. Days and even weeks may elapse before the physician suspects perforation and initiates the proper radiographic search (2). In a study of 48 patients with retroperitoneal-space abscess, Stevenson and Ozeran (3) found that the correct diagnosis was made in less than half of the patients prior to surgery or postmortem examination.

Anterior Pararenal Space Anatomy

In the upper abdomen, three compartments comprise the extraperitoneum: the anterior pararenal space, the perirenal space, and the posterior pararenal space. Altemeier (1) and Meyers (4–7) have described the anterior pararenal space, which lies between the posterior parietal peritoneum and the anterior renal fascia and is open across the midline. The lateroconal fascia, formed by fusion of the anterior and posterior renal fascia, constitutes the lateral boundary. Superiorly, the anterior pararenal space extends to the level of the posterior margin of each hemidiaphragm. Inferiorly, the space extends to the iliac crest level, where it unites with the perirenal and posterior pararenal spaces to form the pelvic retroperitoneum. Fascial planes, therefore, present a temporary barrier to the spread of gas and exudate superiorly and laterally while permitting their passage across the midline and into the pelvis. At the inferior margin, the three com-

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partments communicate freely. The anterior pararenal space contains the pancreas, the duodenum, the vertical colon segments (ascending and descending), and, rarely, the cecum or a retrocolic appendix (Fig. 1). Within the anterior pararenal space a septic process from the colon or appendix may extend to involve the pancreas and duodenum.

Methods

At the Santa Clara Valley Medical Center, 18 patients developed an anterior pararenal space infection consequent to colonic and appendiceal perforation. Surgical exploration confirmed the diagnosis in 17 patients and postmortem examination in 1. The radiographic examinations on these 18 patients were studied retrospectively. All patients had plain abdominal radiographs; 8 had contrast-medium enema examinations; 2 were examined by ultrasonography, 2 by computed tomography, and 3 by urography; 2 gastrointestinal series and 1 fistulogram were done.

In the 18 patients, the anterior pararenal-space abscess resulted from an infected diverticulum in 4 patients, carcinoma necrosis and obstruction in 4, blunt abdominal trauma in 3, retrocecal appendicitis in 3, penetrating trauma in 2, colostomy leak in 1, and a foreign body in 1.

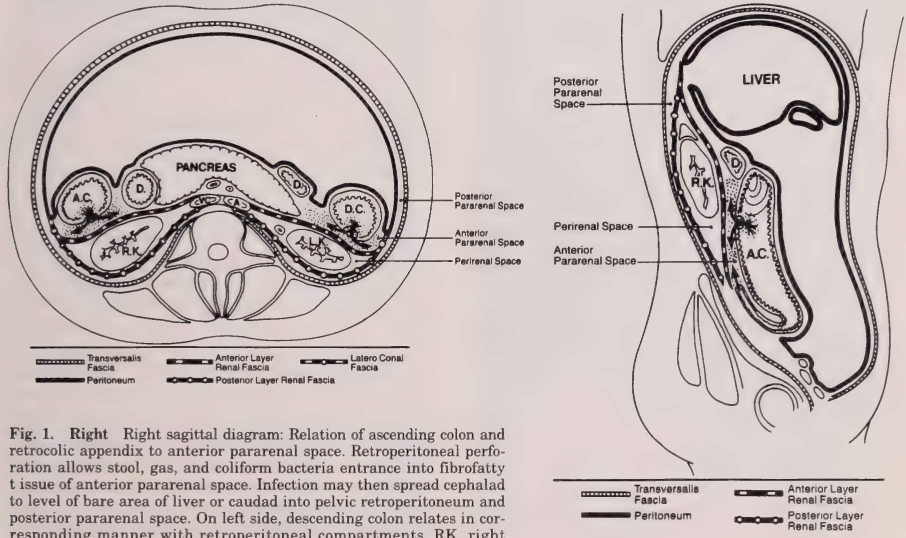
The location of the perforation varied as follows: descending colon in 9 patients, ascending colon in 5, appendix in 3, and cecum in 1.

Results

Abdominal Radiographic Findings. Retroperitoneal mass: A retrocolic or pericolic mass was found in 17 of 18 patients. On the right side, the mass usually displaced the colon anteromedially (Fig. 2); on the left side anterolaterally. In one patient, the mass appeared to encircle the colon wall. The mass also caused anterior and contralateral displacement of the small bowel.

Extraluminal gas: An equally important radiographic finding was the presence of extraluminal gas in 16 of 18 patients. In the majority, this took the form of small bubbles of gas within an abscess (Fig. 3). In 2 patients, the gas appeared as linear streaks; and in one patient, a large collection of gas distended the retroperitoneum.

Properitoneal fat and the abscess: The laterconal fascia separates the anterior pararenal space from the properitoneal fat. On the abdominal radiograph, the properitoneal fat outlined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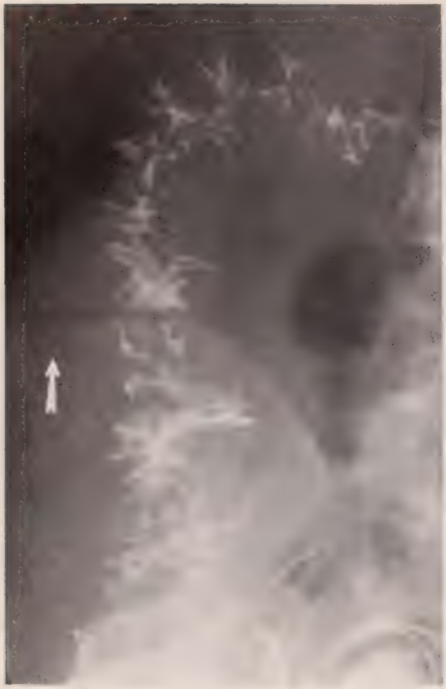
Transversalis Fascia
Peritoneum
Anterior Layer Renal Fascia
Posterior Layer Renal Fascia
Latero Conal Fascia
LIVER
Posterior Pararenal Space
D
R.K.
Perirenal Space
A.C.
Anterior Pararenal Space
Transversalis Fascia
Peritoneum
Anterior Layer Renal Fascia
Posterior Layer Renal Fascia

Fig. 1. Right Right sagittal diagram: Relation of ascending colon and retrocolic appendix to anterior pararenal space. Retroperitoneal perforation allows stool, gas, and coliform bacteria entrance into fibrofatty t issue of anterior pararenal space. Infection may then spread cephalad to level of bare area of liver or caudad into pelvic retroperitoneum and posterior pararenal space. On left side, descending colon relates in corresponding manner with retroperitoneal compartments, RK, right kidney, AC, ascending colon, D, duodenum. **Left** Transverse diagram: position of ascending and descending colon segments in anterior pararenal space. The anterior pararenal space contains pancreas, retroperitoneal duodenum, and vertical colon segments. Space is open across midline and limited laterally by lateroconal ligaments. AC, ascending colon. DC, descending colon. D, duodenum. RK, right kidney, LK, left kidney. A, aorta, VC, vena cava.



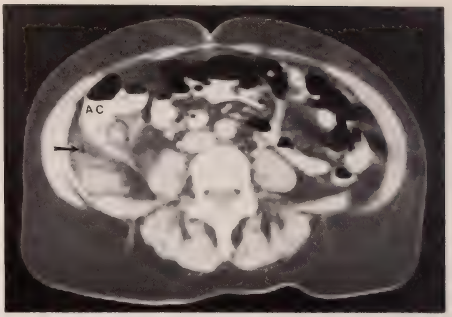


Fig. 2. Left Ruptured retrocolic, retroperitoneal appendix with anterior pararenal space abscess. Postevacuation radiograph of barium enema. Mass containing gas (arrow) lies between ascending colon and properitoneal fat layer. Abscess displaces ascending colon medially and also flattens and widens mucosal folds. **Right** CT. Ascending colon (AC) displaced anteromedially by abscess (A) in anterior pararenal space. Inflammatory process, showing gas bubble (arrow), has spread to posterior pararenal space.

the lateral border of the anterior pararenal-space abscess in 15 of 18 patients. In 3 patients, the inflammatory process obscured the properitoneal fat, indicating that infection had spread from the anterior to the posterior pararenal compartment via the open inferior margins or directly through the fascia, which is not inviolable (8). A lateral gutter abscess or a perirenal abscess will also lie within the properitoneal fat layer; this appearance alone does not confirm anterior pararenal space infection (9).

Ipsilateral psoas and kidney outlines: In only one patient did the abscess obscure the ipsilateral renal outline (in comparison with the uninvolved side), and in 4 patients the ipsilateral psoas was obscured. In no case did the mass displace the adjacent kidney. Because the anterior pararenal-space abscess occupies a separate compartment, it is less likely to obliterate the ipsilateral renal and psoas fat planes. However, in 10 patients, neither the kidneys nor the psoas outlines were visualized.

Hepatic or splenic angle obscuration: The posterior inferior margins of both the liver and spleen indent the fat layer of the anterior pararenal space. Normally the fat-organ interface permits visualization of the organ's posterior inferior margins, or "angle" (10). Infiltrate in the anterior pararenal space might obscure the fat-organ interface in comparison with the normal side. This occurred in only one patient.

Fistulization: In one patient, a descending colon diverticulitis produced a fistula with the third portion of the duodenum via the anterior pararenal space (Fig. 4).

Contralateral spread: Although the anterior pararenal space is open across the midline and inferiorly, gas and exudate had spread to the opposite side in only 2 of the 18 patients.

Ileus: In 11 of the 18 patients nonobstructive small-bowel and large-bowel dilatation was found. In 7 patients, despite extensive retroperitoneal sepsis, no ileus occurred.

Duodenal displacement: Since the duodenum lies in the anterior pararenal compartment, an abscess on the right side could displace the second portion of the duodenum, and an abscess on the left side could displace the duodenojejunal juncture at the ligament of Treitz. No displacement was documented by abdominal radiography, contrast-medium enema, computed tomography, or ultrasonography. However, the proper study to show displacement would be a contrast-medium duodenal study, which was available in only two patients.

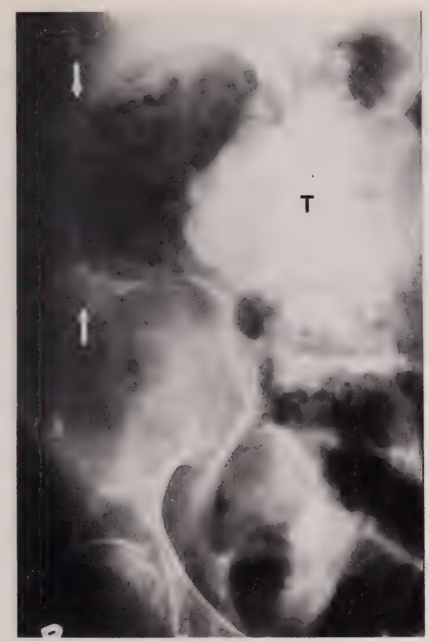


Fig. 3. Retroperitoneal perforation of ascending colon proximal to obstructing carcinoma. This 52-year-old woman refused surgery in favor of laetrile treatment for demonstrated transverse-colon carcinoma. She returned in terminal condition. Abdominal radiograph shows midline tumor mass (T) consisting of transverse-colon carcinoma and matted mesenteric nodes. Mass containing multiple small gas bubbles displaces dilated ascending colon medially. Some gas bubbles lie outside bowel wall (arrows). Autopsy showed that bowel overdistention proximal to obstruction caused ischemic perforation.

Ultrasonography and Computed Tomography. Two patients were examined by ultrasound and 2 by computed tomography. These techniques correctly identified anterior pararenal-space fluid collections in all 4 patients (Figs. 2, 5).

Contrast Colon Study. In 8 of the 18 patients, the colon was examined by contrast-medium enemas. In 5 of 6 patients with colon perforation, the contrast media extravasated. In all patients, the colon study confirmed the presence of an anterior pararenal space mass (Figs. 4, 5). In 2 patients with appendicitis, the contrast medium did not fill the appendix or extravasate. Lack of filling by itself has little significance, as 30% to 40% of normal appendixes do not fill when a contrast-medium enema is done; a completely filled appendix would tend to exclude appendicitis. An appendiceal coprolith was not encountered. Mucosal irregularity representing contiguous inflammatory swelling and edema occurred in 7 of the 8 patients (Fig. 6).

Discussion

In suspected retroperitoneal sepsis, the plain abdominal radiograph obtained in sequential fashion (left lateral decubitus, upright, and supine), will give maximum information (11, 12). A pericolic or retrocolic mass associated with extraluminal gas suggests anterior pararenal-space abscess. Regardless of the radiographic projection, retroperitoneal gas tends to maintain a constant position within the tissues. If overlying bowel makes the detection of abscess difficult, oblique and lateral abdominal radiographs can be helpful.

Other methods of examination include computed tomography (Figs. 2, 5) (13–17), ultrasonography (18–22), and gallium 67 scintigraphy (23–25). The three imaging methods have comparable accuracy and provide complementary information (26). On computed tomography (CT), the abscess appears as a collection of fluid with lower density than the surrounding organs. CT

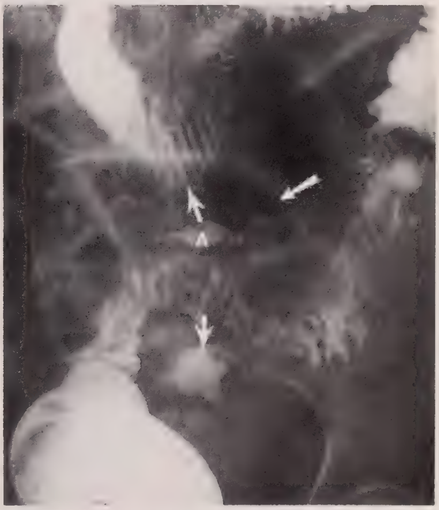
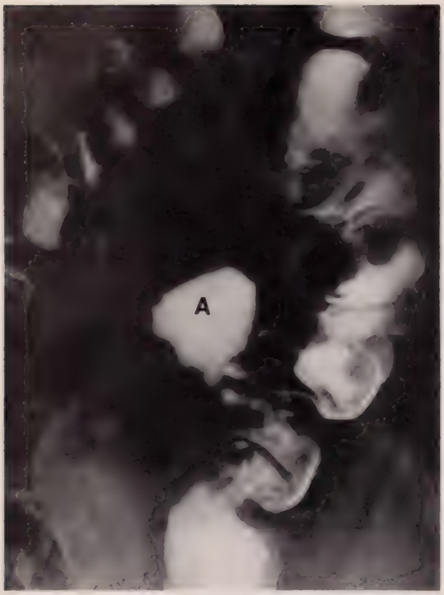


Fig. 4. Descending colon diverticulitis forming retroperitoneal abscess and coloduodenal fistula. This 72-year-old woman experienced nausea, vomiting, abdominal distension, and marked weight loss. Barium outlines fistulous tract from mid descending colon into anterior pararenal space abscess (A), then cephalad into third portion of duodenum. Barium also spread caudad behind sigmoid colon into pelvic retroperitoneum. Direction of fistulous tract shown by arrows.



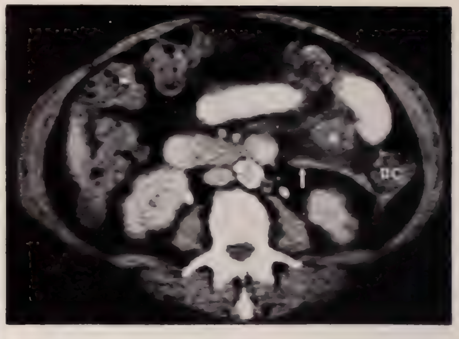


Fig. 5. Ruptured descending colon diverticulum with anterior pararenal-space abscess. Physician palpated mass in left abdomen of this 59-year-old woman. She had no large-bowel symptoms. **Left** Post-evacuation radiograph following barium enema shows barium extravasated into abscess (A) which compresses descending colon against lateral abdominal wall. Colon wall exhibits mucosal irregularity adjacent to abscess. **Right** CT shows abscess (A) in anterior pararenal space compressing the descending colon (DC) and displacing small bowel anteriorly. Inflammatory process has thickened both anterior renal fascia (arrow) and lateroconal fascia.

will also show gas collections within the fluid (8), as well as inflammatory thickening of adjacent fascia and peritoneum (Figs. 2, 5). Both CT and ultrasonography aid percutaneous drainage of abdominal abscesses (27, 28). The culture of coliform bacilli from a needle aspirate suggests a colon or appendix source of infection (29, 30).

The colon contrast study gave helpful information by confirming the findings of the plain radiographic examination: inflammatory mass with mucosal edema in the adjacent colon, extravasation at the site of a colon perforation, and lack of appendiceal filling in acute appendicitis (31, 32), (Figs. 4, 5). The high likelihood of extraperitoneal extravasation makes the use of water-soluble contrast material preferable.

Among the 18 patients I studied, the following conditions caused the anterior pararenal space abscesses.

Diverticulitis: An infected descending-colon diverticulum ruptured to form an anterior pararenal-space abscess in 4 patients. Three of the 4 had minimal symptoms of large-bowel disease, and in these patients, the abscess was detected before the diverticulitis (Fig. 5). In one patient, the abscess formed a fistulous tract with the third portion of the duodenum (Fig. 4). In a follow-up of 294 initially asymptomatic patients with diverticular disease, Boles and Jordan (33) found that 5% developed clinical perforation. In the study reported by Sweatman and Aldrete (34), a correct preoperative diagnosis was reached in only 50% of all patients with perforative diverticulitis.

Carcinoma: Carcinoma caused anterior pararenal space abscess by transmural invasion in 3 patients and by ischemic necrosis proximal to an obstruction in one patient. In all 4 patients, the disease terminated fatally. Carcinomatous colon perforation into the peritoneal cavity or retroperitoneum occurs rarely (35, 36). As with diverticulitis, an anterior pararenal-space abscess may become manifest prior to discovery of the colon carcinoma (29, 31). The differentiation between abscess and retroperitoneal tumor extension can be difficult and, at times, both may be present. In one patient, the abscess extended to involve both the duodenum and pancreas (Fig. 7).

In several reported patients with perforating colon carcinoma, a left perinephric abscess appeared as the initial symptom (31, 37, 38). Presumably, the anterior pararenal-space abscess penetrated the renal fascia to reach the perirenal space.

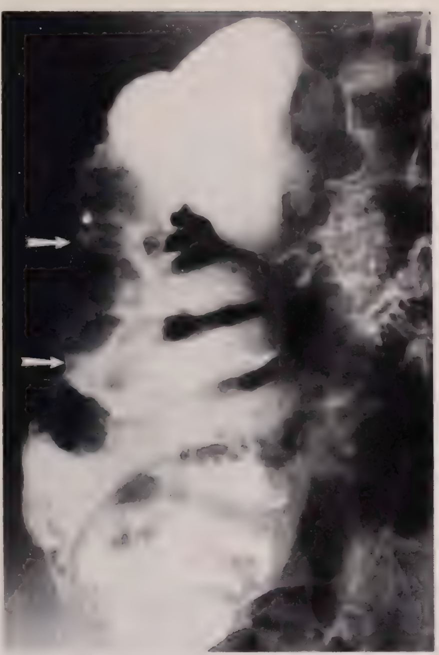


Fig. 6. Perforated retrocolic appendix with anterior pararenal-space abscess altering colonic mucosa. This 33-year-old man had 10-day history of abdominal pain. Radiographs and ultrasonography showed mass containing fluid, but no gas in retrocolic area. On this barium-enema study, mass lies lateral to descending colon. Adjacent to mass mucosal folds are swollen and irregular (arrows). Contrast material does not fill the appendix or extravasate.

Blunt abdominal trauma: Blunt abdominal trauma accounted for three anterior pararenal-space abscesses, one each from perforation of the ascending colon, descending colon, and cecum. A history of injury facilitates the diagnosis as does the finding of bruises and echymoses over the anterior abdominal wall. Colon laceration makes up only 3%–4% of traumatic abdominal injuries, and retroperitoneal perforation is less common (40). In 10 colon injuries due to blunt abdominal trauma, Furstenberg et al (41) found that only 2 resulted in retroperitoneal abscesses.

Retrocecal appendiceal perforation: In 3 patients, the anterior pararenal space abscess followed appendiceal perforation, and on celiotomy, no pus appeared in the peritoneum or lateral gutter.

Considerable variation characterizes the peritoneal attachment of the retrocecal appendix. In the embryo, rotation and fixation of the ascending colon and cecum in the right posterolateral abdomen occurs when both mesenteric peritoneal layers fuse with the posterior parietal peritoneum. During rotation and fixation, the appendix may turn cephalad to lie behind or to either side of the cecum. In a study of 40,001 human appendix specimens, Collins (42) found that 25% were retrocecal. A persistent peritoneal fold forms the appendiceal mesentery, and in the majority of cases, the retrocecal appendix remains within the peritoneum (Fig. 8). Rupture of the intraperitoneal retrocecal appendix may cause a walled-off, lateral gutter abscess and/or diffuse peritonitis (43). In rare instances, the appendix does not retain a peritoneal fold and lies behind the ascending colon (retrocolic), so that perforation leads to anterior pararenal space abscess (44) (Fig. 8). In 250 patients with acute perforating appendicitis, Duyzings et al (45) found only 2 retroperitoneal abscesses.

Penetrating trauma: Knife or bullet wounds to the colon accounted for two anterior pararenal-

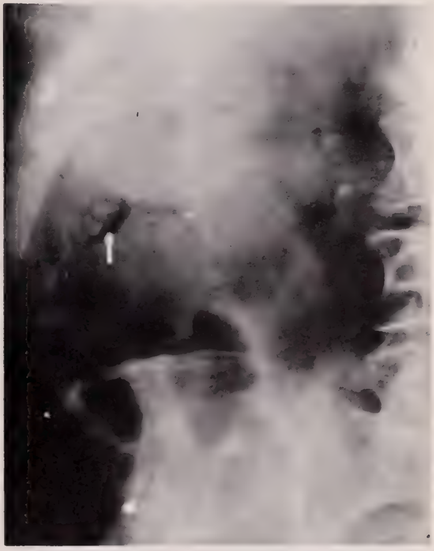
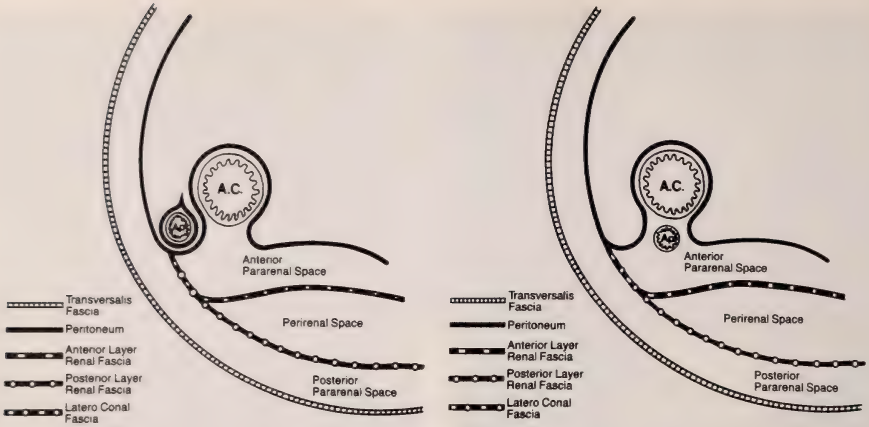


Fig. 7. Carcinoma necrosis and perforation with anterior pararenal-space abscess. This 76-year-old woman had a sigmoid volvulus endoscopically reduced. Following reduction, mass associated with fixed collection of bubbles was found by abdominal radiograph (arrow). Barium-enema study showed carcinoma. At celiotomy, carcinoma had perforated through necrotic area causing retroperitoneal sepsis that involved descending duodenum and pancreas.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Anterior Pararenal Space
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Peritoneum
Anterior Layer Renal Fascia
Posterior Layer Renal Fascia
Latero Conal Fascia
Perirenal Space
Posterior Pararenal Space

Fig. 8. **Left** Intraperitoneal, retrocecal appendix. Appendix extends cephalad adjacent to cecum. An enveloping peritoneal fold serves as mesentery, the meso appendix. When inflamed, appendix in this common position usually perforates into lateral gutter and or peritoneal cavity. A.C., ascending colon; Ap, appendix. **Right** Retroperitoneal, retrocolic appendix. In this rare situation, peritoneal fold does not completely enclose appendix, which lies behind ascending colon in anterior pararenal space. A.C., ascending colon; Ap, appendix.

space infections (Fig. 9). Penetrating abdominal trauma probably causes a relatively large number of retroperitoneal colon perforations, but the current treatment standard of emergency celiotomy, colon diversion, drainage, and repair, presents little opportunity for retroperitoneal abscess to develop (46, 47). A bullet lodging in the retroperitoneum and showing excessive mobility on serial radiographs may indicate a developing abscess—the tumbling bullet sign (48).

Colostomy perforation: In one patient, anterior pararenal space abscess followed spontaneous colostomy perforation. Improper handling of the stoma in a nursing home may have been a contributing factor. Colostomy site complications include perforation as well as hernia, stricture, bleeding, retraction, prolapse, and obstruction. Spiro and Hertz (49) reported on 18 patients with colostomy perforation; none of the perforations extended into the retroperitoneum, 6 were intramural, and 12 intraperitoneal.

Foreign body perforation: In one patient, postmortem study showed the tooth of a comb within the cavity of anterior pararenal-space abscess. Colon perforation by foreign body occurs mainly in the rectosigmoid segments. I was unable to find a report of a foreign-body perforation into the anterior pararenal space. A nonopaque foreign body perforation may be recognized only at surgery or autopsy.

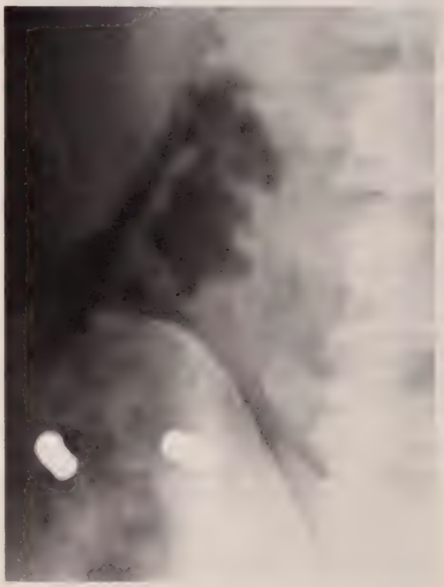

Fig. 9. Gunshot wound, right flank. Ascending colon displaced medially by gas-containing abscess lying between properitoneal fat and colon wall. Gas did not move on patient's change in posture. At surgery, retroperitoneal colon perforation was found and closed.

Rare causes of anterior pararenal-space colon perforation: Reported causes not encountered in this study include stercoraceous ulcers (50, 51), barium enema (52), and granulomatous colitis (53).

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A Diagnostic Approach to Colon Bleeding

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The passage of blood from the rectum is one of the most common signs of colon disease and always indicates the presence of a pathologic process. The origin of any bleeding must be sought and identified, whether grossly visible blood is seen by the patient or is found on fecal occult blood testing by the physician. The many causes for colon bleeding, listed here below, vary from hemorrhoids (1) to colon cancer:

- arteriovenous malformation
- cancer
- diverticulosis
- fissures
- hemorrhoids
- inflammatory etiologies
  - granulomatous colitis
  - infectious agents
  - proctitis
  - ulcerative colitis
- ischemia
- polyps
- radiation injury
- small-bowel sources
  - Meckel's diverticulum
  - tumor
- ulcers, idiopathic
- upper GI source

The clinician has a wide variety of diagnostic approaches available, including the barium enema (2) and sigmoidoscopy, which continue to be of value in the elucidation of problems referable to the large bowel. Because most patients with rectal bleeding do not require the full range of diagnostic procedures available, it is the responsibility of the physician not only to choose the appropriate tests for each circumstance but also to determine proper sequencing of the approach in order to arrive at the correct diagnosis rapidly and economically. This review explores the various modalities available for the investigation of colon bleeding and provides guidelines for their use in a clinical setting.

The initial assessment must be directed toward the rapidity of bleeding, since the approach to the patient with massive rectal bleeding needs to be aggressive; the situation is considerably different when smaller amounts of blood are lost. Massive rectal bleeding has been defined (3) as the passage of copious quantities of bloody bowel movements, requiring two or more units of blood transfusions to maintain the hematocrit at 30%, or bleeding which causes clinical signs of hypovolemia, such as shock, postural hypotension, tachycardia, and pallor. Immediate resuscitative efforts must be directed toward sustaining life while plans are formulated to identify the location of the bleeding site (4). Uncontrolled massive bleeding may be associated with a significant mortality and must be classified as a medical emergency (1, 5–7).

Most patients with rectal bleeding are not "massive" bleeders. The approach to the non-massive-bleeding patient must be individualized and may be less vigorous than when severe bleeding is present. Although the patient's anxiety may be great, there is little immediate threat to life. A small amount of blood from a rectal source, such as hemorrhoids or proctitis, may alarm both patient and physician, since a few cubic centimeters of blood can redden the water in a toilet bowl or create a large stain on clothes or bed linen.

The First Step: Patient's History

The history obtained from the patient is the proper first step in locating the bleeding site. The physician must be thoroughly aware of all the causes of colon bleeding and how they manifest

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themselves as signs which point the way to the use of specific diagnostic tests. A detailed description of the color of the blood, its relationship to bowel movements, and its frequency are the most important determinants of the subsequent approach to the patient. The patient with massive bleeding will have frequent movements with fresh blood and clots. Massive bleeding episodes are usually not accompanied by brown stool, but if, after the first bowel movement, brown stool is present as well as red blood, the site of bleeding is in the left colon, usually in the rectosigmoid region. The explanation for this is that bleeding which originates from the right side of the colon totally admixes with fecal contents; the passage of brown stool separately indicates a more distal origin for bleeding. The clinician must ask the right questions of each patient with rectal bleeding, since the patient will rarely volunteer the specific information needed to localize the site of blood loss.

Among the causes for the passage of blood by rectum is an upper intestinal site with rapid transit time. The origin is most likely to be a peptic ulcer, but certain historical clues should be sought to plan the sequence of diagnostic investigation. When an acute upper intestinal bleed causes the passage of red blood by rectum there is always a large quantity of blood in the small and large intestine. The sudden loss of a massive quantity of blood causes signs and symptoms of cardiovascular instability. Whenever rectal bleeding is associated with evidence of hypovolemia, strong consideration must be given to a proximal source and information indicating a potential upper gastrointestinal bleeding site must be elicited. A history of ulcer disease is important. Melena preceding red rectal bleeding points to a slowly bleeding upper intestinal source with a sudden increase in output. A history of alcoholism or cirrhosis is relevant in considering acute gastritis or the presence of esophageal varices. Upper gastrointestinal bleeding with smaller amounts of blood at a slow flow rate do not stimulate peristalsis and present as melena rather than red bleeding. When left colon bleeding occurs, defecatory responses are frequently stimulated by the presence of blood in the rectum, although the total volume of bleeding may be relatively small. Because of this, bleeding originating from the colon tends to give signs of hypotension late in the course, as opposed to the early development of hypotension when rectal blood loss is a symptom of upper intestinal bleeding.

Patients must be carefully questioned about any bleeding tendencies (8) and especially whether any specific medications such as anticoagulants or aspirin are being taken. Predisposing factors which increase the risks of large-bowel pathology must be sought; among these are a personal or family history of large-bowel polyps or carcinoma. Rectal manipulation and trauma should also be considered (9) in the differential diagnosis of rectal bleeding.

The most common complaint regarding rectal bleeding is of recurrent small amounts of red blood either staining the toilet tissue or in the bowl following defecation. Blood found only on the toilet tissue in association with a normal bowel movement usually has its origin in or around the anal canal but may occasionally originate from a source in the sigmoid colon, accumulating at the anal orifice. Blood spurting (or dripping) into the toilet bowl following normal evacuation is always due to a perirectal lesion, the most common of which is hemorrhoids. When-

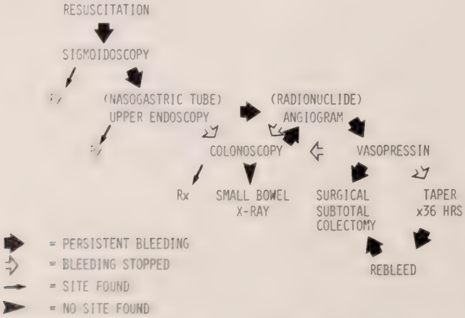

Fig. 1. Schema for diagnosis and therapy of massive lower gastrointestinal bleeding.

ever the symptom of rectal bleeding occurs, it must not be ignored and every effort must be made to locate the source. Small amounts of bleeding attributed to hemorrhoids over years may, without change in character or frequency, be found on investigation to be originating from a rectal cancer or polyp occurring concomitantly with hemorrhoids; blood may drip into the toilet bowl as a low rectal tumor is everted during the act of defecation.

Bright bleeding which stains the bed linen (or clothing), occurring without the patient's awareness and without a bowel movement, is a frightening experience, but in the patient who maintains fecal continence, it is always associated with a site in or adjacent to the anal canal. In this circumstance, the actual amount of blood loss is usually a small volume and self-limited but provokes alarm because of its suddenness. A history of bleeding when the anal orifice is not open implies the presence of hemorrhoids or a rectal fissure.

A streak of blood on one side of a normally formed stool, or spots of blood mixed in with the stool, is less dramatic than free-flowing bright bleeding but of considerably greater prognostic importance. It is probable that the site is in the left colon; a stripe of blood adheres to the formed stool as it passes by the lesion. Blood streaking, spotting, or blood visibly mixed with stool is most often caused by a polyp or carcinoma of the descending/sigmoid colon (10); diverticula rarely, if ever, cause this type of bleeding. Bleeding from a source proximal to the sigmoid colon mixes with stool and may not cause any grossly detectable evidence of blood loss but can be discovered by testing for fecal occult blood.

Bright red blood diffusely coating a normal solid brown stool may occur with radiation colitis (11), even years after the radiation therapy was administered. The rectum, being fixed in position, is the portion of the gut most frequently affected during radiotherapy for pelvic neoplasm. Radiation tissue damage may stimulate neovascularization of the mucosal surface with its propensity to bleed. Proctitis may also cause blood to coat a normal stool, but urgency is an almost invariable accompaniment. Bloody diarrhea, with or without mucus and pus, points to the presence of colonic inflammation, the most frequent cause of which is ulcerative colitis, although other specific inflammatory processes may cause diarrhea and bleeding, such as *Yersinia* enterocolitis, amebiasis, or bacterial infections (12).

Occasionally a patient may report seeing a reddish color in the toilet water around a formed brown stool. This phenomenon is usually due to lysis of red blood cells by the hypotonic water, resulting in the reddish color. A transverse or descending colon site should be suspected, since blood from the proximal colon may thoroughly mix with fecal contents and be invisible.

Rectal pain as a symptom accompanying rectal bleeding allows a more precise diagnosis for the etiology of bleeding. When defecation causes rectal pain and bright red bleeding on the toilet tissue or dripping into the bowl, a fissure or thrombosed or ulcerated hemorrhoid is the predictable site (13).

The previously asymptomatic patient who gives a history of acute abdominal pain followed by loose stools and usually dark red blood is characteristically a victim of a colonic vascular insult (ischemic bowel disease) (14). If ischemia is transient, these symptoms usually subside rapidly over 12–24 hours. Although vascular insufficiency is most frequently associated with atherosclerotic narrowing of blood vessels (15), young women on oral contraceptives may suffer from venous occlusion without any history (16).

Further Steps: Physical and Laboratory Findings

Physical examination. The general physical examination of patients with rectal bleeding may provide additional clues to the origin of blood loss. Blood in the small bowel acts as a peristaltic stimulant and increased bowel sound activity associated with passage of dark blood by rectum is a diagnostic clue suggesting its origin in the upper intestinal tract. Physical examination of the abdomen must be meticulously performed to locate subtle findings: a mass in the abdomen may be associated with a carcinoma; ascites and/or enlarged liver may be evidence of liver disease. Tenderness with or without rebound in the left upper and mid abdomen indicates intestinal ischemia with the left colon characteristically involved.

Contracted blood volume due to acute blood loss almost invariably causes circulatory instability. Pallor, tachycardia, and diaphoresis may be seen. Postural hypotension is common in hypovolemia, which can be clinically assessed, since patients who tolerate massive blood loss while lying supine may, on assuming a sitting position, develop tachycardia and hypotension.

The laboratory. Blood volume determinations are the most accurate parameter for measuring the precise amount of blood loss. Even though the hematocrit does not immediately reflect changes in blood volume, it is valuable for following the rate of bleeding. Elevated blood urea nitrogen may indicate resorption of blood in the upper intestinal tract. Leukocytosis is caused by any inflammatory process (infection, inflammation, or ischemia, for example); however, sudden blood loss may stimulate an immediate bone marrow response with an elevation in the peripheral white blood cell count. Screening tests for a possible bleeding diathesis should be performed, with abnormalities sought in the prothrombin time and platelet count. Tests for the detection of occult blood in the stool should be a regular part of the examination of every patient. A positive result cannot be ignored. These tests are readily and easily performed by either the patient or the physician.

Diagnostic Modalities

Many lesions are responsible for rectal bleeding, and all of them must be considered in each patient who has this symptom. Many sources can be considered and discarded as untenable during the course of history-taking. Bleeding from the upper intestinal tract and right colon can be ruled out in the patient who gives a history of bright red blood dripping into the toilet bowl following defecation but must be given stronger consideration when the history is of the passage of dark red or maroon stools. In spite of a history consistent with a rectal source of bleeding, a lesion of the more proximal colon must be strongly suspected when there is, in addition, anemia or a positive test for occult blood. A carefully directed history must be extracted from the patient who has bloody diarrhea and cramps. When the previously asymptomatic patient develops these symptoms, an important differential diagnosis hinges on the history of cramps and abdominal pain preceding the bloody bowel movements; severe abdominal pain followed within minutes by bloody evacuations are characteristic of an ischemic vascular insult. On the other hand chronic diarrhea, cramps, and bleeding are more indicative of an inflammatory bowel disease (17).

The diagnostic procedures available for the investigation of colonic bleeding are varied and include digital-rectal examination, proctosigmoidoscopy, barium enema x-ray examination, colonoscopy, radionuclide scintigraphy, angiography, gastric aspiration with nasogastric tube, upper intestinal endoscopy, upper gastrointestinal and small bowel x-ray examination, and surgery.

Given the array of diagnostic procedures which can be performed, the physician must decide which should be offered to each patient, and what should be the sequence of examinations. A detailed medical history and a knowledge of the possible etiologies of bleeding will point to the proper diagnostic procedures that will be necessary in each patient and yet be cost effective so that not every test is ordered in every patient.

Digital Rectal Examination. As part of the physical examination, every patient should have a digital rectal examination. If inordinate pain is elicited upon introduction of the well-lubricated finger into the anal canal, a fissure should be considered as the etiology of bleeding. Indeed, during the rectal examination a foreign body may be discovered. In elderly, infirm patients the digital examination may reveal a mass of impacted stool causing a stercoral ulcer. A coarsely granular feeling of the mucosa should arouse the suspicion of proctitis. Rectal carcinoma can be palpated as a firm, polypoid, or ridgelike mass.

The examining glove should be inspected once it has been withdrawn from the anus to derive further information for the differential diagnosis of the bleeding site.

The presence of black melanotic stool usually implies that bleeding is coming from high up in the intestinal tract, proximal to the ligament of Treitz. This is not always true, since blood placed in the cecum during appendectomy has been reported to cause melena (18) if the first bowel movement occurs more than 72 hours following instillation of blood. However, in practical terms, it is unusual for a bleeding site in the right colon to produce a tarry stool and yet have a slow transit time of 3 days from the cecum to the rectum. Black material on an examining glove should be tested for the presence of blood, since iron ingestion may cause an appearance similar to that of melena.

Dark red blood on the examining glove indicates a source proximal to the hepatic flexure but may originate from the upper gastrointestinal tract as well.

The observation of brown stool and red blood is characteristic of bleeding from the left colon.

Occasionally, the digital examination may lead to an entire change in the approach to the patient, as when a history of fresh red bleeding is obtained from the patient but dark maroon blood is identified on the examining glove, indicating a more proximal site.

Sigmoidoscopy. A sigmoidoscopic examination should be performed on every patient being investigated for rectal bleeding. In addition to allowing the physician to identify a bleeding site or see a lesion, visualization of the mucosal surface in this area may reflect the status of the entire colon.

If copious red blood is accumulating, anoscopy should be performed with a separate instrument, since bleeding from hemorrhoids and fissures may be difficult to identify with a standard 10″ rigid proctosigmoidoscope. The entire circumference of the anal canal can be much better observed using the anoscope with its oblique wide-caliber opening. Through the sigmoidoscope, one may evaluate mucosal patterns and determine the presence of proctocolitis, hemorrhoids, polyps, and carcinoma of the rectosigmoid region. In the presence of proctitis, and frequently with hemorrhoidal bleeding, the instrument may reach above the bleeding site, giving a high degree of diagnostic accuracy.

Whenever sigmoidoscopy is performed for acute bleeding, it must be accepted by the clinician that blood from the rectum may reflux proximally and upon its return may be misinterpreted as evidence of a bleeding site "above the reach" of the sigmoidoscope. This is a difficult problem and may only be resolved by passing a colonoscope through the area of bleeding and identifying that there is a distal origin for blood loss. Blood may reflux up to the area of the mid to upper descending colon (4) from a hemorrhoidal site in a vigorous, healthy young person whose tight rectal sphincteric musculature prevents fecal (and blood) incontinence.

Barium Enema X-Ray. Persistent bleeding, or the finding of positive occult blood in the stool, should be investigated with a detailed history, digital rectal examination, sigmoidoscopy, and air-contrast barium enema x-ray examination. The double-contrast barium enema will discover the majority of lesions causing rectal bleeding (19), and proper therapy may be initiated on the basis of the diagnosis discovered on barium enema.

If a polyp is found on the x-ray examination, its size and location can be assessed and electrodiathermy may be prepared at the time of colonoscopic examination so that polypectomy may be performed. If polypectomy is to be performed in a hospital, the information gained from a barium enema will permit hospitalization arrangements to be made in advance and the diagnostic colonoscopy may then be combined with a therapeutic option.

Frequently, the barium enema will reveal a carcinoma which does not require colonoscopic verification; surgery should be the next procedure.

Colon cancer is one of the most common cancers in the United States (20) and, although the etiology of rectal bleeding may be explained by sigmoidoscopy, the symptoms which stimulate the patient to enter the health care system provide sufficient reason to have the patient's entire colon examined with a barium enema x-ray. The barium enema is an excellent general screening test for colon pathology and can in most instances detect significant polyps, carcinoma, and abnormalities of the large bowel.

Occasionally, no lesions are found during the standard diagnostic work-up, including the x-ray examination. In the patient with colonic bleeding whose history indicates that a specific bleeding site exists, colonoscopy should be performed if no site can be identified radiographically (21–23).

The barium enema plays no role in the management of patients with acute massive rectal bleeding (24), since barium will coat the bowel wall and preclude the subsequent use of either angiography or colonoscopy. Another reason not to use barium in investigation of massive acute bleeding is that most patients will be bleeding from diverticula or arteriovenous malformations, which cannot be diagnosed by routine radiography. For many years there was a belief that barium in an enema form helped to "plug" a bleeding site and was therefore useful in the approach to colonic bleeding (25). This has not been shown to have any scientific basis and, at the present time, a barium enema is not considered to be of benefit either diagnostically or therapeutically in the patient who is actively bleeding.

Colonoscopy. The colonoscope has been demonstrated to reach the cecum in a high percentage of cases (92%–95%) with or without the use of fluoroscopic control (10, 26). Even the most tortuously shaped colon yields to the well-trained endoscopist, and only a few patients cannot be totally intubated. Failures may be encountered in patients with colons fixed by previous pelvic surgery or diverticular disease. During the course of acute bleeding, specific identification of any lesion is much more difficult than in the well prepared, nonemergency examination. Colonoscopy is of great importance in the investigation of patients with chronic, unexplained rectal bleeding (1, 7). When colonoscopy is performed under these circumstances—that is, "routine" diagnostic maneuvers, including barium enema, fail to reveal a lesion—approximately 30%–40% of patients will have a specific lesion discovered by endoscopy (1, 23, 27–29). Several studies (Table) reveal that approximately 15% of patients with unexplained bleeding will have a colon polyp; approximately 10% will be bleeding from a carci-

TABLE
Colonoscopy in Unexplained Rectal Bleeding

Reference	No. Pts	% Lesions	% Polyps	% Cancer	% IBD*
Teague et al (1)	215	41	14	13	7
Tedesco et al (23)	258	42	15	11	7
Brand et al (27)	306	30	14	8	4
Hunt (28)	561	42	14	11	10
Swarbrick et al (29)	239	40	16	10	10

* IBD = inflammatory bowel disease.

noma; 5% will have an arteriovenous malformation; and 7% will have previously undiagnosed inflammatory bowel disease.

Radionuclide Scintigraphy. Technetium 99m sulfur colloid scanning is a relatively new noninvasive diagnostic modality that provides rapid information on whether a lesion is actively bleeding at the time of the procedure (30, 31). The technique involves intravenous injection of technetium radioisotope which rapidly clears from the circulatory system but, in the actively bleeding patient, leaves a collection of intraluminal radioactive material at the bleeding site. This is a sensitive, highly reliable test for the presence of bleeding but is relatively nonspecific; that is, a site in the right upper quadrant may originate in the colon or in the duodenal bulb. Sequential examinations may increase specificity by demonstrating appropriate peristaltic flow of radioactive material in the pattern of the colon or small bowel.

The ease of this examination and its rapidity (information may be obtained in 15 minutes) have prompted some centers to refuse angiography unless active bleeding has been demonstrated on an immediately preceding radionuclide scan. Intermittent bleeding may be detected using technetium-labelled autologous human red blood cells (32).

Angiography. Abdominal angiography is helpful in brisk bleeding when the rate of blood loss is more than 0.5ml per minute (33). In the presence of such active bleeding, extravasation of dye from the vascular component to the intraluminal space occurs leaving a persistent stain after the vascular blush disappears. When bleeding is at a slower rate insufficient dye collects to be of diagnostic value. The procedure requires an expert angiographer and precise localization of the bleeding site may be accomplished, although a specific diagnosis may not be possible (34). In non-bleeding patients, an arteriovenous malformation may be identified as a vascular blush or by the presence of a large draining vein.

Gastric Aspiration by Nasogastric Tube. It has been reported that in all patients with gastrointestinal bleeding, the passage of a nasogastric tube provides fairly accurate information concerning the presence of an upper gastrointestinal bleeding site (35). In a series of 1,190 patients, only 1% were found to have an inaccurate diagnosis of an upper intestinal bleeding site as determined by the passage of a nasogastric tube with aspiration of bloody gastric contents. However, in that same journal, an editorial (36) pointed out that, when specific patients were selected as being at high risk from upper gastrointestinal hemorrhage, as many as 20% of bleeding duodenal ulcers yielded no evidence of bloody reflux into the stomach and therefore yielded a spuriously negative nasogastric aspirate.

Upper Gastrointestinal Endoscopy. With the advent of smaller caliber, more easily tolerated upper intestinal panendoscopes capable of examining the entire esophagus, stomach, and duodenum, passage of a flexible fiberoptic endoscope into the stomach is not much more traumatic than the passage of a nasogastric tube. Whenever upper gastrointestinal bleeding is seriously considered as a cause for colonic hemorrhage, an upper gastrointestinal endoscopic examination should be the first line of investigation, since information obtained from passage of a nasogastric tube may be misleading (36). Whenever upper gastrointestinal bleeding occurs, the endoscopic examination has been shown to be the best diagnostic procedure for the location of the site of bleeding (37). An endoscopic examination may be performed quickly at the bedside of the bleeding patient and yields considerably more diagnostic information than either passage of a nasogastric tube or an upper gastrointestinal barium x-ray series.

Upper Gastrointestinal X-Ray Series. Apart from angiographic visualization of small-bowel blood vessels, no new technologic advances have been developed for visualizing the small intestine. For patients with undiagnosed recurrent slow bleeding, a small-bowel x-ray series should be carefully performed. Tumors of the small bowel are unusual but may be detected by barium studies. In the acutely bleeding patient, barium should not be given, for it interferes with subsequent diagnostic evaluations, such as angiography and intestinal endoscopy.

Surgery. Exploratory surgery for massive intestinal bleeding is rarely performed because of the spectrum of diagnostic studies currently available (19, 24). Angiography has demonstrated that bleeding caused by diverticulosis frequently occurs from the right side of the colon, although there are many more diverticula in the sigmoid colon. During massive bleeding episodes either radionuclide scanning or angiography should be performed following history, digital rectal examination, and proctosigmoidoscopy. When these studies are unavailable or unrevealing, "blind" subtotal colectomy may be necessary and can be a life-saving procedure.

Sequence of Diagnostic Tests

The basic diagnostic evaluation in every bleeding patient consists of the history, digital rectal examination, and sigmoidoscopy.

After the basic evaluation has been performed, the type and extent of further investigation will depend on the assessment by history and physical examination of whether major or minor bleeding has occurred.

Nonmassive Acute Rectal Bleeding

An important differential symptom in patients with a history of frequent red bowel movements without signs of hypotension is whether abdominal pain is present. Painless bleeding is caused by hemorrhoids, cancer, polyps, diverticular disease or arteriovenous malformations, whereas abdominal cramps and pain may be associated with ischemia. The patient should be asked specifically whether bleeding is accompanied by the passage of brown stool. If there is brown stool and red bleeding, the site is in the left colon or rectum. Acute, copious bleeding from the left colon will not be mixed with formed stool and is frequently from hemorrhoids or left-sided diverticular segments. Patients may not be able to answer the question whether brown stool is present, and the physician must then decide whether the sudden passage of bloody bowel movements indicates bleeding from the right or left colon. Fortunately, most bleeding ceases spontaneously no matter what the origin.

Blood Dripping into Toilet Bowl after Defecation. This symptom indicates a site of bleeding in or near the anal canal. If pain occurs, there may be a fissure which was torn open by the passage of stool; this can be seen with an anoscope or proctoscope. In the absence of pain, the cause is most likely hemorrhoids which have become everted with the passage of stool. The history which usually accompanies this symptom is one of recurrent bleeding episodes that stop spontaneously. Bleeding seen on the toilet tissue following defecation is often of similar perirectal origin and should have the basic diagnostic evaluation. However, not all such bleeding should be attributed to hemorrhoids, since proctitis, rectal and sigmoid polyps, and carcinoma may occasionally present in this fashion. Every patient must have a rectal examination and sigmoidoscopy to explain this symptom. **Additional procedures: barium enema optional, but preferable, to examine the whole colon.**

Bright Red Blood Staining Bed Linen or Undergarments without Defecation. Bleeding of this nature, without an active attempt to open the rectal sphincter, is always associated with a bleeding site proximal to the rectal sphincter muscles. This means that the site is in or external to the anal canal. The usual cause is a ruptured hemorrhoid, and the site may be seen on direct inspection with an anoscope. Even though the cause of such bleeding is obvious on proctosigmoidoscopic examination, all patients should have a barium enema x-ray so that lesions elsewhere in the colon will not be overlooked. **Additional procedures: barium enema.**

Rectal Bleeding with Abdominal Pain. When bloody bowel movements are associated with the sudden onset of abdominal pain in a previously asymptomatic patient, the most likely cause is ischemic bowel disease. Sigmoidoscopic examination, if negative, should be followed by angiographic evaluation. A subsequent barium enema may reveal the typical "thumb-printing" along the edges of the colon. The most frequent location for ischemia is in the left colon; however, sigmoidoscopic examination may reveal evidence of a dusky mucosa when ischemia occurs low in the left colon. **Additional procedures: angiography; subsequent barium enema.**

Rectal Bleeding and Diarrhea. Most diarrheal diseases begin without bleeding. Ulcerative colitis usually has a nonbleeding phase before characteristic symptoms develop. The sigmoidoscope may enable the correct diagnosis to be made and, if the patient is quite ill, therapy may then be instituted without additional diagnostic procedures. In the absence of toxicity, a barium enema should be the next diagnostic procedure to permit definition of the entire colon and for evaluation of the extent of disease. **Additional procedures: stool cultures; barium enema.**

Chronic Colonic Bleeding

Streaks of Blood on Surface of Stool. Blood streaks on stool surface are a significant symptom that requires a satisfactory explanation. Whenever this complaint is obtained, careful attention must be given to the strong possibility that a lesion exists in the area of the rectosigmoid colon. Although a hemorrhoid or fissure may cause this symptom, a cancer or polyp in the left colon is the more common cause of a linear streak of blood on the surface of a formed stool. This type of bleeding does not occur as a result of diverticulosis. If a lesion is seen on double-contrast barium enema, a decision must be made concerning proper therapy. If no lesion is identified, a colonoscopic examination must be performed. The sigmoid colon may be a difficult area for the radiologist to fully visualize so that some hidden lesions may be expected. Patients who are x-ray negative with a significant history have a 15% incidence of polyp and a 10% incidence of carcinoma. A "significant" history means (a) blood streaking or spotting the stool; (b) a positive test for occult blood; (c) unexplained iron deficiency anemia. **Additional procedures: barium enema; if negative, colonoscopy.**

Spots of Blood Mixed with Stool. This symptom has the same significance as streaks of blood on the surface of the stool and should be investigated in a similar fashion.

Red Blood on Toilet Tissue, associated with Blood Emanating from Surface of Brown-Colored Stool. This symptom is almost always associated with an organic lesion in the descending or distal transverse colon. Blood adheres to a superficial portion of the stool and, being present in small amounts and mixed with surface mucosa, is not visibly red but hemolyzes and causes a reddish color. As the stool passes the anal canal, it may leave a film of blood which may be seen on the toilet tissue. **Additional procedures: barium enema; if negative, colonoscopy.**

Occult Blood in Stool, No Visible Bleeding

Finding occult blood in stool in the absence of visible bleeding usually indicates a lesion in the right colon which loses small amounts of blood that mix with the stool and are then not visible to the naked eye. In these instances, cancer of the colon is a common cause, but polyps, solitary ulcers, inflammatory bowel disease, and arteriovenous malformations may also cause occult bleeding. Even if hemorrhoids are seen on sigmoidoscopy, the bleeding should not be attributed to them, and a barium enema must be performed; if negative, colonoscopy should follow. Angiography or radionuclide scanning is not usually helpful in these circumstances, since the rate of bleeding is low. **Additional procedures: barium enema; if negative, colonoscopy.**

Massive Bleeding with Signs of Hypovolemia

To meet the criteria for massive bleeding, the patient must have copious quantities of bloody bowel movements with either clinical evidence of hypotension or the need for two units of blood transfusion to maintain the hematocrit at 30%. Bleeding of this severity may be caused by a variety of conditions, but usually involves the three major causes

- diverticular bleeding
- arteriovenous malformation
- upper gastrointestinal bleeding

although carcinoma may occasionally bleed massively (38, 39). **Additional procedures: radionuclide scintigraphy and/or angiography. Upper gastrointestinal endoscopy if an upper intestinal bleeding site is suspected.**

Diverticular disease accounts for the majority of all massive colon bleeding (40, 41) and 3% of all patients with symptomatic diverticular disease will sustain a massive rectal hemorrhage (6, 42, 43). Although there are many more diverticula in the sigmoid colon than the right colon, diverticulosis of the right colon has been demonstrated to be the origin of rectal bleeding in a substantial number of cases (44, 45). The diagnosis of massive bleeding from diverticular disease is best made on radionuclide scanning or angiography, since the presence of blood in the bowel tends to obscure visualization during the use of the colonoscope. Acute rectal bleeding tends to stop spontaneously (38). Only 5% of patients with massive bleeding from diverticular disease will require emergency surgery to stop bleeding (46).

Arteriovenous malformations usually occur in the right colon and may be associated with the degenerative process of aging. These A-V communications tend to bleed suddenly without warning and produce no symptoms for the patient other than frequent bowel movements of dark red blood. The bleeding is usually voluminous and may stop as suddenly as it started, but it may require resection of the right colon to control hemorrhage. Localization of the bleeding site requires radionuclide scanning or angiography (44, 47) where the demonstration of a prominent draining vein from an arteriovenous malformation makes a diagnosis more definite. Rarely are large-bowel arteriovenous malformations associated with other vascular anomalies in that patient. Forty-eight hours following the acute bleeding episode, the patient may be safely colonoscoped using a full preparation, including cathartic and enemas. The small arteriovenous malformations appear to the endoscopist as a collection of fine reddish blood vessels localized to a specific area on the wall of the ascending colon (48–50). These malformations may be either small or extensively interlaced, covering a wide area of the right colon.

Although angiography is quite helpful in localizing the site of massive rectal bleeding, colonoscopy has been reported to be of variable benefit (51).

Rossini (52, 53) states that blood in the bowel acts as a cathartic, and the multiple evacuations associated with acute, voluminous rectal bleeding cleanse the colon so that enemas are not necessary. It is frequently helpful to pass a sigmoidoscope with a wide-caliber suction apparatus to evacuate clots in the rectal ampulla where they tend to accumulate. The colonoscope may be passed under direct vision up to the bleeding lesion or beyond the area of bleeding into a nonbloody segment of the colon (54). As soon as the instrument has passed beyond the segment of active bleeding, the procedure need not be continued, since identification of a bleeding area is the desired end point of the examination, not full and total colonoscopy.

Other investigators have found that blood clinging to the walls of the colon during episodes of active bleeding obscure mucosal markings and make it difficult to ascertain which of multiple bloody areas may be bleeding (7, 55). Cleaning the bowel sufficiently for adequate visualization is almost impossible. It has been advocated that a dental Water Pik be adapted to use through the biopsy port of the instrument with the ability to squirt a powerful jet of water at the mucosa to cleanse it of blood and residue (56).

Bleeding from the upper intestinal tract is usually accompanied by the passage of dark red stool or port-wine-colored bowel movements, but bright red bleeding may be present (3). Whenever dark blood is passed by rectum, the site is almost always the proximal colon or upper intestinal tract. If the bleeding site is a Meckel's diverticulum (57) or originates elsewhere in the small bowel, there may be no clues to that etiology (42).

On the other hand, upper intestinal bleeding may be accompanied by an episode of melena for 1–2 days prior to the episode of brisk bleeding from a source such as a peptic ulcer. Patients should be questioned about previous bowel movements as well as ingestion of drugs known to be associated with upper gastrointestinal bleeding, such as salicylates, antirheumatic therapy, reserpine or corticosteroids. A history of peptic ulcer disease must be carefully elicited, and special attention should be directed toward the presence of alcoholism, previous liver disease, previous intestinal bleeding episodes, and any other factors which may have predisposed to upper intestinal bleeding.

In patients with massive rectal bleeding from an upper intestinal source, a considerable amount of blood is present in the intestinal tract with a rapid transit time. This leads to hyperactivity of the small bowel with easily audible borborygmus and signs of hypovolemia, such as postural hypotension, tachycardia, and pallor. Blood in the intestinal tract may cause an elevated blood urea nitrogen.

In spite of a strong suspicion of an upper intestinal bleeding site, a sigmoidoscopic examination should be performed in every patient to permit observation of the rectal mucosa (38). It is possible that the frequent passage of bloody stools, although dark in color, may be the initial manifestation of ulcerative colitis which can be diagnosed through the sigmoidoscope. Following a negative sigmoidoscopic examination in a patient highly likely to have an upper intestinal bleeding site, an upper intestinal panendoscope should be passed into the stomach and duodenal bulb to ascertain the presence of bleeding.

Summary

A step-by-step schema has been presented for the investigation of patients with the symptom of rectal bleeding. The cornerstone of an accurate diagnosis rests on a thorough and complete history obtained from the patient. Although each of the many possibilities must be considered in every patient with rectal bleeding, the differential diagnosis may be markedly narrowed by an accurate history and pinpointed by the appropriate diagnostic procedure. A stepwise approach to every patient with rectal bleeding will enable the physician to arrive at a prompt and precise diagnosis in an efficient and economic manner.

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Miscellaneous

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Staging of Lymphoma and Testicular Carcinoma

William E. Torres, M.D., and Michael E. Bernardino, M.D.

A variety of staging systems for lymphomas have been proposed in the last 30 years. The drive behind such detailed classifications results from the enormous amount of information available concerning cellular pathology, immune mechanisms, and new treatment modalities.

Once there has been a biopsy diagnosis of lymphoma, the search for all sites of involvement is begun. The armamentarium available to aid in staging includes clinical, radiologic, laboratory, and surgical techniques. Radiographically, there are a variety of methods available to evaluate the patient with lymphoma, including radioisotope scanning, ultrasound, whole lung tomography, computed tomography (CT), and bipedal lymphography. With the advent of CT, however, whole lung tomography, ultrasound, and radioisotope scanning have become infrequent. Evaluating and staging the patient with lymphoma has been made infinitely easier with the use of CT, and we may hope for future advances with nuclear magnetic resonance (NMR). A time can be envisioned when these modalities will replace staging by lymphography and surgery. With CT, the extent of both nodal and extranodal disease, both above and below the diaphragm, can be assessed.

Hodgkin's and Non-Hodgkin's Lymphoma

It is a well-established fact that Hodgkin's disease and non-Hodgkin's lymphoma differ in both initial sites of presentation and subsequent patterns of spread (1, 2). Although the diagnostic workup is similar, it differs in some respects. In a study by Glatstein et al, 82% of patients with Hodgkin's disease showed disease in the primary area alone or in the primary area plus contiguous regions; only 8% of Hodgkin's disease patients had noncontiguous spread of disease (3). Patients with Hodgkin's disease have a higher incidence of cervical, mediastinal, and splenic hilar node involvement, the nodular sclerosing type of Hodgkin's showing the highest incidence of mediastinal involvement.

Two factors appear to be associated with the increased risk of abdominal node involvement when there is known disease above the diaphragm: presence of systemic symptomatology and number of involved mediastinal nodes. As the number of mediastinal nodes affected increases, so does the likelihood of disease below the diaghragm (2).

Non-Hodgkin's lymphomas tend to show more involvement of the mesenteric, retrocural, and hepatic hilar nodes. Mesenteric nodes are involved in more than 50% of non-Hodgkin's patients. Patients with the nodular type of non-Hodgkin's lymphoma have a higher incidence of mesenteric node involvement than patients with the diffuse type. In non-Hodgkin's patients with para-aortic lymphadenopathy, mesenteric nodal involvement occurs in approximately four fifths of patients with the nodular type of disease and in one half of patients with the diffuse type of non-Hodgkin's lymphoma (1).

When there is upper abdominal lymphadenopathy in the patient with Hodgkin's disease, the liver and spleen should be examined carefully for spread of the disease. The spleen is the most common site of intra-abdominal disease in the patient with untreated Hodgkin's disease. Hepatic involvement by lymphoma is identified in more than 50% of patients who die from either Hodgkin's or non-Hodgkin's lymphoma (4, 5). A histologically positive spleen in a Hodgkin's patient at laparotomy can be considered presumptive ev-

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idence of liver involvement, even in the face of a negative liver biopsy (3).

Splenomegaly alone in Hodgkin's disease is not a reliable sign of disease. One third of patients with Hodgkin's or non-Hodgkin's lymphoma may not have splenomegaly. The incidence of liver involvement in patients with untreated Hodgkin's is low, approximately 5%, and is almost always associated with splenic involvement. In contrast, a significantly enlarged spleen in patients with non-Hodgkin's lymphoma indicates a high probability of lymphomatous involvement. Splenic involvement, more common than hepatic involvement, is seen in approximately 30% of patients with non-Hodgkin's lymphoma at their initial presentation; hepatic involvement is seen in 15% (1–3).

Computed Tomography. In recent studies, CT has been shown to be the method of choice in the initial evaluation of the patient with lymphoma. It is as sensitive as lymphography in detecting early or minimal lymph node involvement and, in 95% of cases, the lymphangiogram can be eliminated.

An additional advantage of CT is its usefulness in areas previously inaccessible to radiologic study, namely, the internal iliac group of nodes in the pelvis, nodes in the porta hepatis, splenic and retrocural, and the high para-aortic nodes. Computed tomography can demonstrate the full extent of the total nodal volume involved in the disease process (Figs. 1, 2).

The obvious advantage of CT is its ability to detect disease not previously suspected either radiologically or clinically (Fig. 3). Staging can be drastically altered by discovery of previously unsuspected lesions in the lungs or in the mediastinum; this would necessitate combination chemotherapy rather than radiation. In non-Hodgkin's lymphoma, with a greater incidence of mesenteric lymph node involvement, the field of radiation can be assessed more accurately to include all sites of the disease (1, 2).

Computed tomographic examination of the liver and spleen has been disappointing in both Hodgkin's and non-Hodgkin's lymphoma. The use of intravenous contrast material does not substantially improve the evaluation of lymphomatous involvement of the liver and the spleen. In a series of 323 patients with known lymphoma, the sensitivity of CT for hepatic involvement was only 57%. Microscopic involvement does occur; thus, a certain percentage of splenic and hepatic involvement will not be demonstrated radiographically (Fig. 4). This study was performed on second-generation scanning equipment, and with drip infusion of intravenous iodine. No precontrast scans were obtained (6).

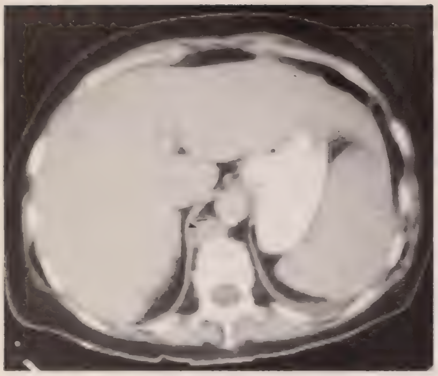
Until recently, the only completely reliable method of detecting small foci of involvement was by laparotomy and splenectomy. Ethiodized Oil Emulsion 13 (EOE 13) is a newly developed intravenous liposoluble contrast medium which has shown a tenfold increase in the detection of splenic lesions. EOE 13 is initially taken up by normal reticuloendothelial tissue similar to the radionuclide scanning agents. It increases the attenuation coefficients of the normal liver and spleen. This increases the contrast differential between normal visceral tissue and pathologic processes. Thus, EOE 13 and newer experimental agents have shown themselves to be extremely useful in detecting abnormalities in liver and spleen (5, 7).

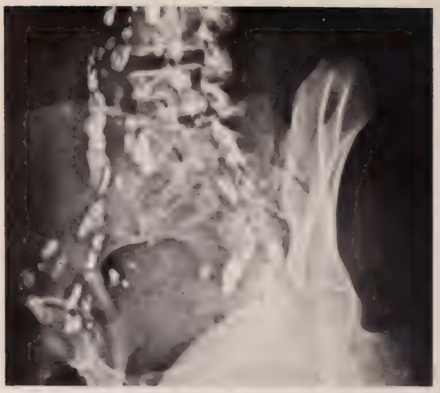
The disadvantage of CT lies in its inability to detect disturbances in the internal nodal architecture. Therefore, CT would be of little value in the evaluation of the patient without nodal enlargement, but with the typical "foamy" appearance of involved nodes as seen at lymphangiography. This usually occurs in early-stage Hodgkin's disease.

In a recent study by Oliver et al (8), 365 CT examinations in 125 patients with a histologic diagnosis of lymphoma were studied. Clinical correlation immediately preceding the follow-up CT examination was obtained in 100 patients. The overall correlation between findings on CT follow-up studies and clinical course was 91%. It was demonstrated that if a patient's clinical course is at variance with CT findings, the area in which to look for recurrence is in the central nervous system.

Another finding by Oliver and colleagues (8) was diminished nodal or visceral lesion size with associated decreased internal attenuation or mesenteric "stranding" (Fig. 5). The actual significance of the change in the internal architecture is unknown. A hypothesis is that there is destruction of tumor cells within the involved node, with subsequent fatty or fibrous replacement (8).

One of the relative disadvantages of CT is its cost in monitoring the effectiveness of therapy. Some institutions provide a limited study (three to four slices), substantially reducing cost without sacrificing needed information. Realizing that the lymphomas are a diffuse group of disorders, the physician must tailor the CT examination to the patient. Without question, the more rapidly progressive processes should be followed more fre-





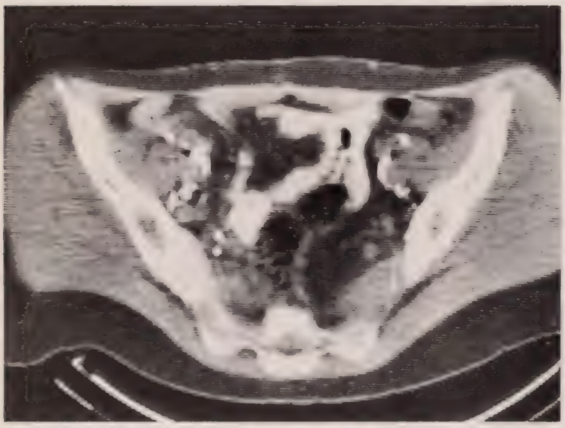


Fig. 1. Above left Patient with lymphoma. CT shows enlarged retrocural node (arrow). Lymphangiography would not pick up abnormal nodes in this location.

Fig. 2. Woman, 33 years old, with Hodgkin's disease. **Above right** Lymphangiogram shows enlarged nodes but no evidence of disease. **Left** CT demonstrates adenopathy in the pelvis.

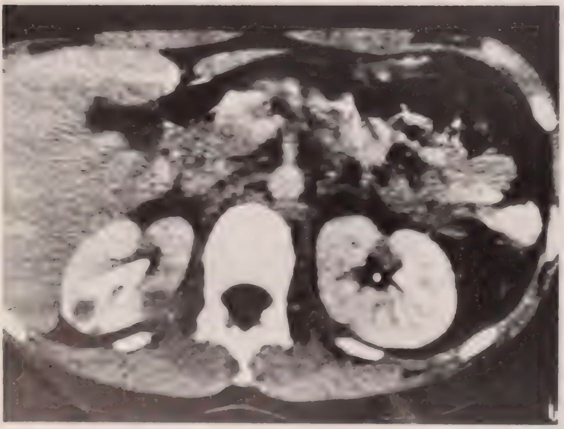


Fig. 3. Patient with lymphoma; involvement of kidneys demonstrated.

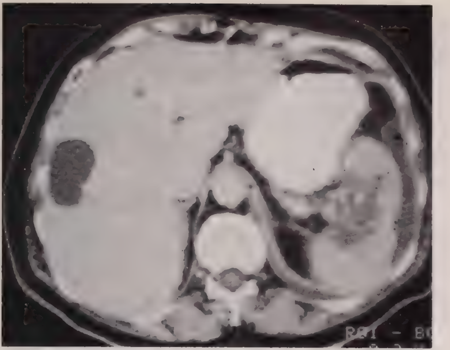


Fig. 4. CT exam in patient with lymphoma demonstrating large splenic and liver lesion.

quently. The major concern with a limited study is whether the disease process will extend to noninvolved sites while remaining unchanged in the initial site of presentation. In a study by Thomas et al, the correlation between the limited CT and the complete CT was found to be greater than 98% (9).

Another possible pitfall of CT is the problem of residual nodes or masses following therapy. However, masses or nodes that are enlarged following therapy do not always represent viable disease. Fine-needle percutaneous aspiration is an accurate and safe means of diagnosing retroperitoneal or abdominal masses to determine viable tissue. The accuracy of this method is 64% in lymphoma. If the needle biopsy is not adequate for diagnostic purposes, laparotomy may be necessary prior to additional therapy (Fig. 6) (10, 11).

CT has several advantages over lymphangiography. It can demonstrate the extent of para-aortic nodal disease, especially in enlarged or bulky masses or if the disease is above the level of the renal vessels. It is noninvasive and can demonstrate disease outside the para-aortic area, such as high para-aortic, mesenteric, retrocural, splenic, and hepatic hilar nodes and the internal iliac group in the pelvis. It can also be of value in evaluation of the liver and spleen (1, 2, 4–7).

Many lymphoma patients are followed by abdominal plain films for reasons of simplicity and low cost. This type of follow-up is not without problems, since the amount of contrast material within nodes decreases with time (12). Also, follow-up films only evaluate the contrast-filled nodes; thus, large masses in other abdominal or pelvic areas can be missed.

Testicular Neoplasms

In males aged 15 to 34, testicular neoplasms are the most common solid tumor and account for 12% of all cancer deaths in this group (13). Histologically, the germ-cell testicular neoplasms are composed of different cell types and are divided into seminomatous and nonseminomatous types. The nonseminomatous testicular carcinomas are further divided by elements within the tumor into embryonal, teratomatous, choriocarcinomatous, or mixed types.

Initial histology is an important factor in survival. In a report from M. D. Anderson Hospital, the overall three-year no-evidence-of-disease rate was 82% for pure seminoma, 62% for teratoma, 55% for mixed teratomatous tumors, 39% for embryonal carcinoma, and 26% for choriocarcinoma (14).

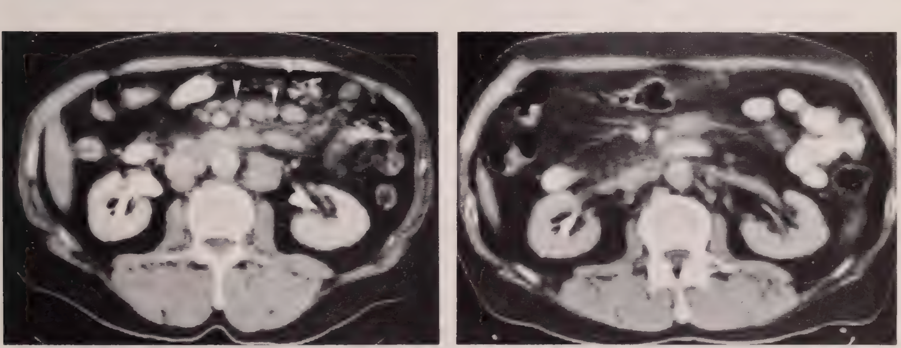
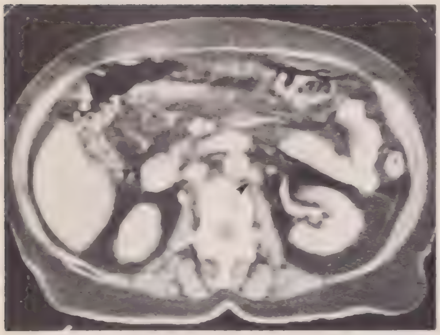


Fig. 5. Lymphoma patient. **Left** Pretherapy: mesenteric nodes (arrows). **Right** Posttherapy: mesenteric nodes demonstrated to be gone. Patient now has residual "stranding" in the mesentery.



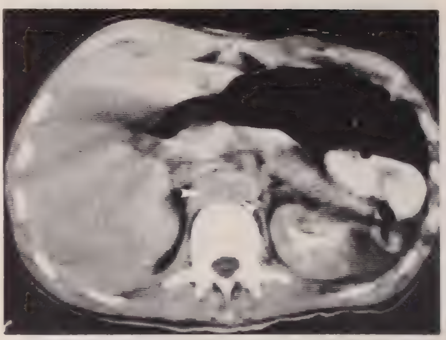


Fig. 6. **Left** Lymphoma patient, posttherapy. Enlarged node to left of aorta (arrows). Only further study can determine if this represents viable tissue.

Fig. 7. **Right** Young male with testicular carcinoma. CT shows enlarged nodes in retroperitoneum (arrows).

Testicular tumors tend to spread by the lymphatic system rather than by hematogenous routes. The testicular lymphatics drain primarily into a series of sentinel nodes located between T-11 and L-4. These nodes are more laterally placed than are the lumbar nodes, which are opacified by bipedal lymphangiography. Once the sentinel nodes are involved, the lumbar nodes become involved, either bilaterally or unilaterally. Once the retroperitoneum is involved, seminoma goes on to involve the mediastinum and the supraclavicular nodes. This is followed by hematogenous dissemination to the lungs, liver, and brain (13, 14).

Anatomically, the drainage of the right and left testicles differs. The left testicle drains at the L-1 through L-2 level into lateral para-aortic nodes just below the left renal vein. On the right, the main channel terminates at the L-1 through L-3 level between the renal vein and aortic bifurcation. Drainage from the right testis can end directly in the left lateral para-aortic nodes. Even though both testes have lymphatic drainage to ipsolateral external iliac nodes, isolated involvement of external iliac, femoral, or inguinal nodes is seen most often after prior surgery or biopsy when the primary pathway has been altered (13, 14).

The seminomatous tumors are radiosensitive to the degree that even large nodal masses are curable by relatively low dose radiation; lymphadenectomies are therefore generally not performed. If reduced fields are to be used during radiation therapy, it is important to have accurate localization of the site and margins of a tumor mass.

The nonseminomatous tumors of the testes, much less radiosensitive, generally require combined therapy. Radiotherapy, while effective in controlling masses less than 2 cm, is ineffective in larger masses in the retroperitoneum. Lymphadenectomy, from the renal hilus to the iliac region, is the alternative in controlling retroperitoneal disease. Extension of the procedure up to the level of the diaphragm is done in patients with retrocural nodal involvement.

The major advantage of lymphangiography over CT is its ability to detect architectural changes within nonenlarged nodes. The accuracy of lymphangiography is in the range of 85%; however, metastasis may be missed, either because of microscopic size or because the lymph nodes which contain the metastasis may not be opacified by the bipedal lymphangiogram (15).

Since the advent of CT, the retroperitoneum can be evaluated accurately with high resolution (Fig. 7). In a study by Thomas et al, the overall accuracy of CT was 89%, with a true positive ratio of 90%. These authors attributed the high accuracy and sensitivity of CT to the large, bulky masses that testicular tumors tend to produce with concurrent early nodal enlargement (14). CT can also detect extralympathic sites of involvement which would alter therapy.

Summary

Computed tomography should be the initial diagnostic procedure in the staging of testicular carcinoma; the lymphangiogram provides an alternate method of staging patients whose CT is equivocal, either because of body habitus or a technically poor study. In CT scanning following therapy, it is often impossible to distinguish benign lesions such as fibrotic dead tumor from vi-

able malignancy because CT can only detect gross changes in anatomy. Following therapy, the now sterile tumor may not return to normal size secondary to fibrosis or necrosis, even with successful therapy. Therefore, a residual mass may be present, and the posttherapy scan may appear unchanged from pretherapy. Percutaneous needle aspiration and surgery are methods available to establish the viability of the tumor (16).

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Life-Threatening Gastrointestinal Complications of Leukemia

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Abstract

Life-threatening gastrointestinal complications of leukemia are more common than is generally appreciated. Their increasing incidence is the result of newer, aggressive treatment methods and increased patient life span. Nine percent of all leukemic patients seen at the University of Arizona Health Sciences Center from January 1979 through March 1983 developed at least one significant gastrointestinal problem during the disease course. These complications included necrotizing enterocolitis, diffuse leukemic infiltration of the gut, severe bowel hemorrhage, appendicitis, abscess formation, generalized peritonitis, *Candida* esophagitis, esophageal necrosis, splenomegaly with gastric and esophageal varices, and bile duct obstruction. In almost all instances, radiographic methods were diagnostic. Rapid, specific diagnosis of gastrointestinal complications of leukemia is imperative since prompt medical and surgical intervention can be life-saving. These complications should no longer be considered preterminal. Aggressive medical and surgical therapy was life-saving in 62% of our patients. Moreover, even in those patients who eventually succumbed to their disease, significant palliation resulted.

Leukemia represents 4% of all cancer deaths and is the leading cause of death from malignancy for all patients younger than age 30 (1, 2). Five-year survival is only 4% for acute forms and 16% for all other types (2). With evolving modern chemotherapy, antibiotic therapy, transfusions, and radiation treatment, the survival rate is increasing. However, complications secondary to the therapy and the more prolonged course of the disease are also increasing.

A variety of life-threatening gastrointestinal complications of leukemia (1, 3–13), usually classified as quite rare and preterminal events (1, 3), have been reported. However, rapid recognition of one of these complications coupled with specific aggressive therapy can frequently save the patient's life and restore reasonable health.

This report emphasizes the increasing frequency, common radiologic presentations, and favorable prognosis of these processes, given early recognition and prompt medical or surgical intervention.

Subjects and Methods

We performed a computer survey of all patients treated for leukemia from January 1979 through March 1983 at the University of Arizona Health Sciences Center (AHSC). The clinical and radiographic records of those patients who were known to have developed one or more significant gastrointestinal problems during the course of their disease were then studied in detail. We specifically directed our attention toward the type of gastrointestinal problem, the method of diagnosis, and the relationship of the problem to the patient's leukemia and antileukemic therapy.

Results

We identified 142 leukemic patients (47 children, 95 adults) seen at AHSC from January 1979 through March 1983 (Table 1). Thirteen (9%) presented with at least one significant gastrointestinal complication. This may be a low estimate, since all gastrointestinal problems in the 142 patients surveyed may not have been found. Of these 13, 6 (13%) were children, 7 (7%) were adults aged 21 and over (Table 2). Initially only 2 of the 13 were in clinical remission and were

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TABLE 1
Leukemic Patients at University of Arizona Health Sciences Center 1979–1982

		Children		Adults*	
Type of leukemia	Total	Male	Female	Male	Female
1. Reticuloendothelial	5			1	4
2. Plasma cell	1				1
3. Acute lymphoid	33	17	10	5	1
4. Chronic lymphoid	14			4	10
5. Acute myeloid	62	9	6	26	21
6. Chronic myeloid	23	4		10	9
7. Myeloid	3			2	1
8. Unspecified	1	1			
	142				

* Age 21 and over.

not receiving antileukemic therapy; 11 were being actively treated for their leukemia.

In these 13 patients, 4 had more than one complication (total complications, 18). Five of the 13 patients (38%) died of their leukemia. Three of the deaths were in part directly related to gastrointestinal complications. The other two patients showed marked palliation as a result of aggressive treatment, and their deaths were not related to their gastrointestinal problems. Even those dying directly from their gastrointestinal disease received significant short-term palliation from appropriate therapy.

Radiographic means coupled with clinical and laboratory data led to the correct diagnosis in 14 (78%) of the 18 complications. Clinical findings alone were diagnostic in four instances (22%). The radiographic methods used were plain abdominal radiographs (5 patients), barium studies (4 patients), ultrasound (3 patients), CT (2 patients), arteriography (2 patients), and excretory urography (one patient). Six patients had more than one imaging study (Table 2). In one patient with cecal necrosis (typhlitis) and another with acute appendicitis, plain radiographs of the abdomen were unremarkable and the diagnosis was made at laparotomy. In almost all other instances, imaging played a key role in proper patient diagnosis.

TABLE 2
Gastrointestinal Complications in 13 Leukemic Patients

Pt. No.	Sex & Age		Leukemia Type	GI Complication	Method of Diagnosis
1	Female	14	Acute myelogenous	Typhlitis Died 1 month later	History, physical exam
2	Female	2	Promyelocytic	(a) Pseudomembranous colitis; *Candida* overgrowth (b) Perirectal abscess Died 2 weeks later	(a) Physical exam; plain abdominal films; stool culture (b) Physical exam
3	Female	4	Acute lymphoblastic	Ureterocolonic fistula, abscess	Intravenous pyelogram
4	Female	26	Acute myeloblastic	Esophageal candidiasis and necrosis Died 5 days later	Esophagram (Fig. 6); endoscopy
5	Female	61	Acute myelogenous	Diverticulitis with abscess	CT, ultrasound, barium enema
6	Male	26	Acute myelogenous	Common bile duct obstruction by chloroma	CT (Fig. 3), ultrasound
7	Male	19	Acute myelomyelocytic	(a) Acute appendicitis with abscess (b) Toxic megacolon, abscess (c) Jejunal ulceration with hemorrhage	(a) History, physical exam (b) Plain films (Fig. 7.) (c) Arteriography
8	Male	20	Acute myelogenous	(a) Pseudomembranous colitis (b) Typhlitis	(a) Stool culture (b) Barium enema (Fig. 2.)
9	Male	14	Acute myelogenous	Leukemic infiltration of small bowel Died 3 months later	Plain films, upper GI series (Fig. 1.)
10	Male	69	Chronic myelogenous	Esophageal *candidiasis* Died one month later	Esophagram (Fig. 5.)
11	Male	45	Hairy cell	Massive splenomegaly	Ultrasound, plain films
12	Male	55	Acute myelogenous	Megacolon secondary to chemotherapy	Plain films
13	Female	66	Chronic myelogenous	(a) Splenomegaly (b) Esophageal varices	(a) Plain films (b) Arteriography

Discussion

Leukemia not only affects the hematopoietic system directly but also involves many organs and tissues elsewhere in the body. The gastrointestinal tract is one such area that frequently undergoes extensive pathologic changes, produced primarily by the disease process or secondarily by its treatment (5, 6) (see list of complications and Table 3). Lymphoid tissue is widely distributed in the gut and mesentery, especially in the ileum, appendix, and colon, and leukemic infiltration is not uncommon in later stages of the disease. Almost 50% of children with acute leukemia who die in relapse show at least microscopic evidence of bowel infiltration at postmortem (5).

In an autopsy survey of 148 acute and chronic leukemic patients of all ages, Prolla and Kirsner found gross leukemic lesions in the gut in 25% of patients. Moreover, mycotic infections occurred in 16% of patients, and severe gastrointestinal hemorrhage took place in 18%, resulting in the death of eight patients (6). The most common lesion was hemorrhagic necrosis of various portions of the gut. Also present were a variety of surgical problems including appendicitis, cecal perforation, liver abscesses, and peritonitis from hemorrhagic proctocolitis (6).

Dewar et al, reviewing leukemic patients undergoing emergency laparotomy, found a similar occurrence of gastrointestinal lesions and complications at autopsy (7). They described four basic types of pathologic lesions: (a) hemorrhagic necrosis, (b) leukemic infiltrates, (c) agranulocytic necrosis, and (d) fungal overgrowth (7). A fifth type was a mixture of the other four, typically hemorrhagic necrosis and leukemic infiltration.

Leukemic infiltrate (Fig. 1) can result in plaquelike thickening of the bowel wall, raised nodular lesions, diffuse mucosal and submucosal infiltration, polyp formation, and ulceration (1). Ulceration results from direct leukemic infiltration and necrosis as well as fungal and bacterial overgrowth. Secondarily, perforation, peritonitis, gross hemorrhage, abscess formation, and septicemia with bacteremic shock can take place. The stomach, ileum, and colon are most commonly involved.

Severe hemorrhage frequently accompanies the other complications because of profound thrombocytopenia secondary to the disease process or its therapy. Massive hemorrhage due to thrombocytopenia is often a contributing cause of death (7).

The entire range of gastrointestinal complications can be seen in all forms of leukemia, acute or chronic (Table 2), but incidence and severity may vary with the type (5, 11). In the lymphocytic types, the bowel wall involvement tends to be confined to the mucosa; in the myelogenous forms, the infiltrates may be more widespread throughout the length and thickness of the bowel (4).

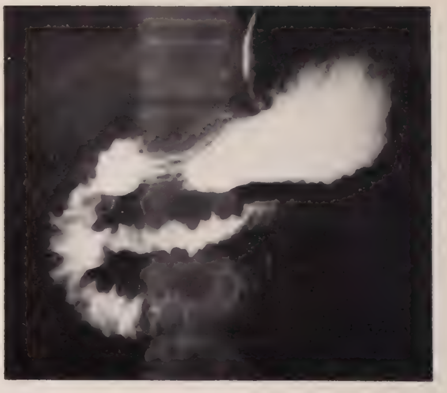


Fig. 1. White boy, age 14, with acute myelogenous leukemia. Upper GI series shows thickening to wall and mucosal folds of jejunum from leukemic tumor infiltration.

Typhlitis (Fig. 2) is a rare but well-recognized complication of lymphoma and leukemia. It is localized inflammation of the terminal ileum, appendix, or cecum and is commonly a preterminal event in treated childhood leukemia (3). It has been reported in adults and appears to have an increasing incidence (3, 9, 11). A recent report of five patients by Abramson et al stressed its occurrence early in the course of childhood leukemia, particularly in patients with acute myelogenous leukemia (11). It is almost always seen in patients undergoing intensive chemotherapy and rarely involves direct leukemic infiltration of the bowel wall (11).

In the majority of cases, the pathogenesis of typhlitis appears to be cecal ulceration from bacterial overgrowth secondary to an altered immune state from chemotherapy (3, 11). Mucosal edema and ulceration may involve the total thickness of the bowel wall and may lead to necrosis, perforation, and abscess formation (Fig. 2). Bacterial, fungal, and even viral infection is usually present, the most common organisms being *Pseudomonas, Candida,* and, at times, cytomegalic virus (11). While typhlitis has been given a special name and described separately from other gastrointestinal complications of leukemia, it is

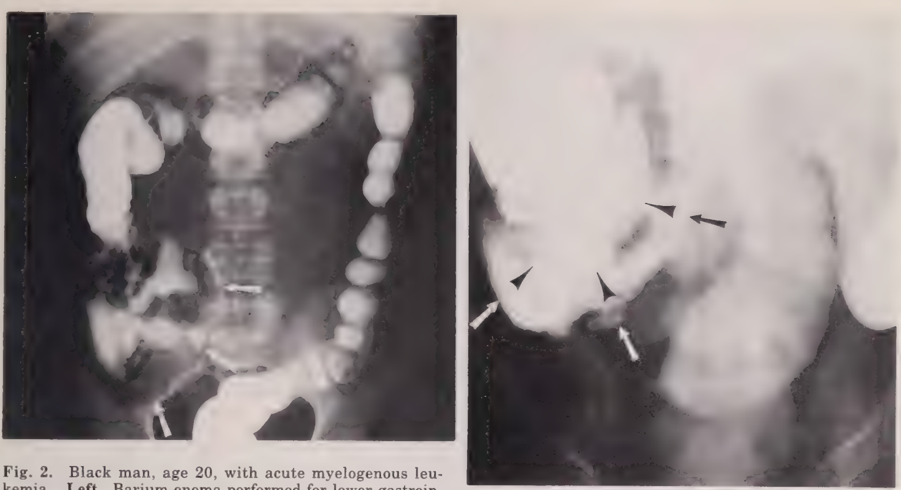


Fig. 2. Black man, age 20, with acute myelogenous leukemia. **Left** Barium enema performed for lower gastrointestinal bleeding shows gas pocket (white arrows) in expected location of cecum and **Right** Extravasation of barium outside bowel into gas pocket; wall of cecum (black arrowheads), confines of gas pocket and extravasated barium (arrows).

best considered a localized form of the infectious complications of leukemia.

Etiology. The etiology of most leukemic gastrointestinal complications is, we believe, threefold (Table 3): (a) primary invasion by leukemic cells, (b) altered immune state with profound neutropenia from the leukemia itself and antileukemic drugs, and (c) direct and indirect gastrointestinal toxic effects of chemotherapy.

Massive invasion of the bowel, spleen, liver, biliary, and pancreatic structures by leukemic cells can cause bowel or bile duct obstruction or predispose to intussusception (Figs. 1, 3, 4). On rare occasions, leukemic distension of the liver and spleen may lead to infarction or rupture. Chemotherapy may directly produce necrosis and weakened areas in the bowel wall while destroying the underlying cancer cells (7). Bacterial, fungal, or viral overgrowth can invade the bowel and produce ulceration, necrosis, perforation, or pseudomembrane formation (Figs. 5–7).

These effects may be further enhanced by a patient's weakened immune response and neutropenic state. Microscopic vascular insufficiency, vitamin deficiencies, thrombocytopenia, neutropenia, and miscellaneous coagulation abnormalities contribute to mucosal petechiae and hemorrhage (7). A variety of perianal lesions such as fistulas, abscesses, inflamed anorectal tissues, and hemorrhoid formation may occur (7). Bacterial or fungal invasion of the bloodstream can lead to distant abscess formation and eventual endotoxic shock.

Antibiotics further complicate the picture by altering the normal gut bacterial flora; steroids, antimetabolites, and folic acid antagonists predispose toward agranulocytic lesions, especially in the cecum (7). The cecum may be particularly susceptible to injury because of its relative stasis, its easy distensibility, its predisposition toward mucosal ischemia, and its normally high bacterial count (11).

Chemotherapeutic agents affect the gastrointestinal system by altering the patient's immune state and by predisposing toward acid peptic disease. They can also produce a neurotoxic effect on the gut (11, 12). Vincristine, in particular, may incite a reversible megacolon that probably results from autonomic ganglia damage (12). Motility disorders, including aperistalsis of the esophagus, have also been observed with this agent. Other agents directly attack the bowel, causing vascular changes and ischemia (12). In addition to profound nausea and vomiting, ulceration, pancreatitis, adynamic ileus, hepatitis, and hemorrhagic colitis have been associated with various antileukemic drugs (7, 13).

Radiographic Findings. Radiographic findings of gastrointestinal complications of leukemia are protean.

Life-Threatening
Gastrointestinal Complications of Leukemia

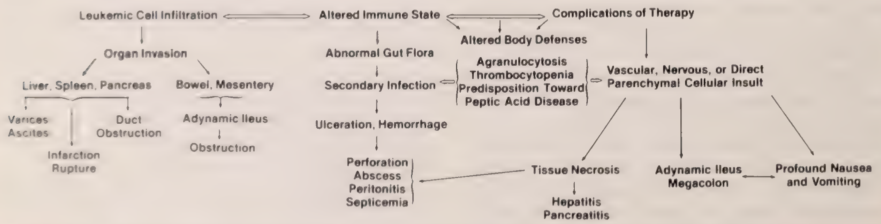
- Infections
  - Toxic megacolon and its complications
    - Severe hemorrhage
    - Perforation—peritonitis and abscess formation
    - Overwhelming septicemia
  - Typhlitis—gangrenous inflammation of cecum and terminal ileum
    - Perforation with abscess formation
    - Hemorrhage
  - Pseudomembranous enterocolitis
    - Part of disease course
    - Complication of antibiotic therapy
  - Other
    - Appendicitis—perforation, abscess formation, peritonitis
    - Diverticulitis—perforation, abscess formation, peritonitis
    - Fungal and bacterial mucosal overgrowth—ulceration, hemorrhage, perforation
    - Perianal inflammation—fistulas, fissures, abscesses, cellulitis, infected thrombosed hemorrhoids
    - Cytomegalic and other virus invasion, especially in cecum
    - Liver, spleen abscess
- Leukemic invasion of bowel
  - Obstruction
    - Adynamic ileus
    - Mechanical blockage by tumor or massive blood clots
    - Intussusception
  - Diffuse ulceration
    - Perforation—peritonitis, abscess formation
    - Severe hemorrhage
    - Bacterial and fungal overgrowth
  - Protein-losing enteropathy
  - Pneumatosis intestinalis
- Hemorrhage
  - Thrombocytopenia
  - Diffuse ulceration—oozing of blood from the gut
  - Localized ulceration into major blood vessel
  - Hematoma formation
- Liver, spleen, and pancreas
  - Obstruction of biliary and pancreatic ductal system by leukemic tumor
  - Diffuse invasion by widespread tumor—liver and spleen
    - Infarction
    - Rupture
  - Formation of esophageal and gastric varices
    - Obstruction of portal system by tumor or clot
    - Splenomegaly with varices from increased blood flow
  - Ascites
- Drug-related bowel complications
  - Vincristine-induced megacolon
  - Steroid-induced peptic ulcer disease
  - Infections secondary to low white blood cell count and generalized immune suppression
  - Neurotoxicity and direct gut toxicity

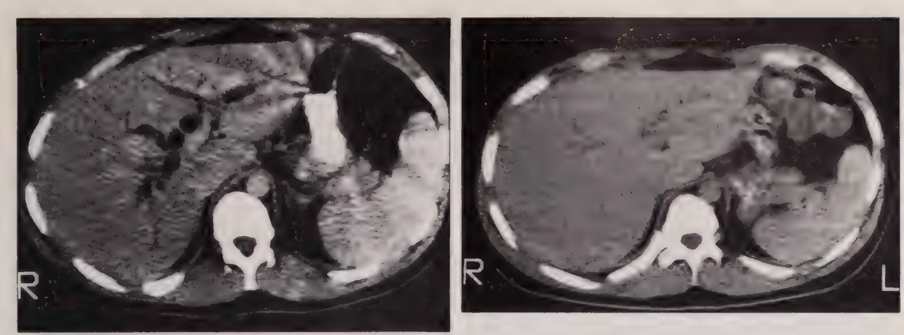
On plain radiographs, abscesses are characterized either by the presence of an unusual localized gas collection, with or without associated fluid levels, or by the presence of a fecallike mottled gas pattern (Fig. 7). On CT and ultrasound, they appear as localized fluid and/or gas collections. Gallium 67 or indium 111 radionuclide scans are frequently positive and aid in diagnosis and localization.

Leukemic infiltration of the gut causes mucosal and bowel wall nodularity and thickening on plain films and barium studies (Fig. 1). Ulcerations from peptic acid disease, necrosis, tumor invasion, or antileukemic therapy are evident on barium studies. Active bleeding sites may be demonstrable by arteriography or radionuclide studies. Bowel perforations are recognized by the presence of a pneumoperitoneum, retroperitoneal gas, or spillage of contrast material outside the gut on barium or water soluble contrast examinations (Fig. 2).

Liver and spleen enlargement are evident clinically, as well as on plain radiographs, CT, ultrasound, and radionuclide studies. Esophageal and

TABLE 3
Etiologic Flowchart: Gastrointestinal Complications of Leukemia


Leukemic Cell Infiltration
Altered Immune State
Complications of Therapy
Altered Body Defenses
Organ Invasion
Abnormal Gut Flora
Liver, Spleen, Pancreas
Bowel, Mesentery
Agranulocytosis
Thrombocytopenia
Predisposition Toward
Peptic Acid Disease
Vascular, Nervous, or Direct
Parenchymal Cellular Insult
Secondary Infection
Varices
Ascites
Duct
Obstruction
Adynamic Ileus
Obstruction
Infarction
Rupture
Ulceration, Hemorrhage
Perforation
Abscess
Peritonitis
Septicemia
Tissue Necrosis
Hepatitis
Pancreatitis
Adynamic Ileus
Megacolon
Profound Nausea
and Vomiting



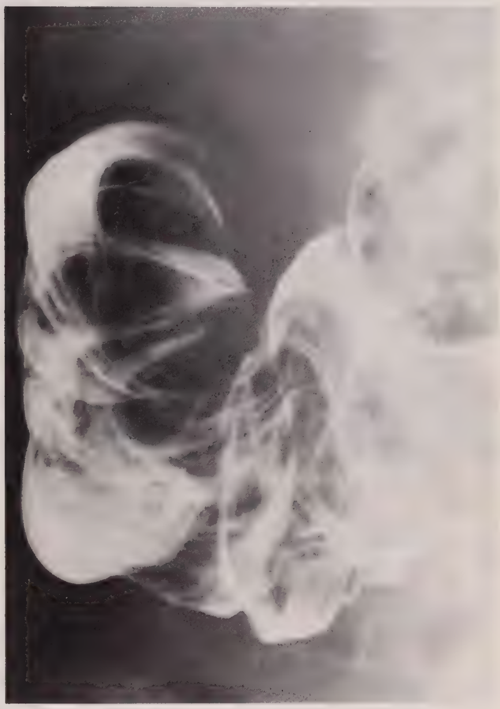
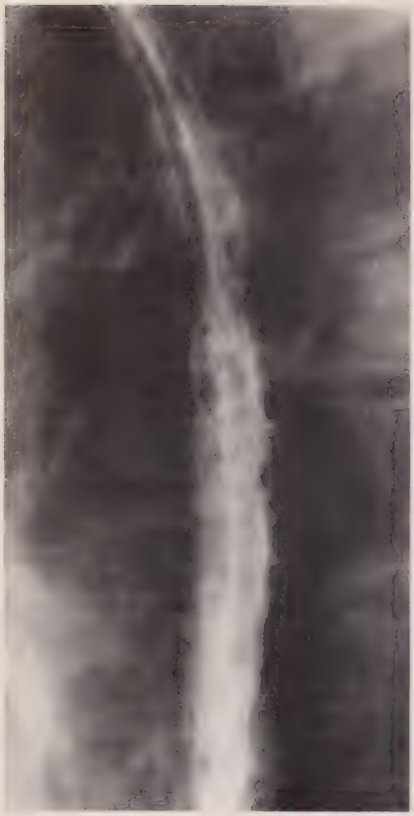


Fig. 3. White man, age 26, with acute myelogenous leukemia and three-week history of jaundice. **Above left** CT scan through liver demonstrates bile duct dilatation. **Above right** CT scan at same level one month later after chemotherapy and localized radiation therapy to a slightly enlarged head of pancreas thought to be infiltrated by leukemic tumor; bile duct dilatation has resolved.

Fig. 4. **Right** White girl, age 16, with acute myelogenous leukemia. Barium enema performed because of sudden severe abdominal pain shows intussusception, found at surgery to have arisen from terminal ileum and perhaps caused by diffuse leukemic infiltration of bowel. No leading mass.

gastric varices produce typical fluoroscopic contrast filling defects and have a characteristic angiographic appearance. Space-occupying liver and spleen lesions and bile duct obstruction (Fig. 3) are best demonstrated by CT, ultrasound, or nuclear medicine studies. Ultrasound and CT can show minute quantities of ascites; massive ascites is readily evident on plain radiographs and physical examination. Plain radiographs coupled with barium studies readily diagnose mechanical bowel obstruction, adynamic ileus, and intussusception (Fig. 4).

Candidiasis and other infectious overgrowths of the esophagus produce spasms, ulcerations, and irregularly marginated filling defects on esophagography (Figs. 5, 6). Although pseudomem-



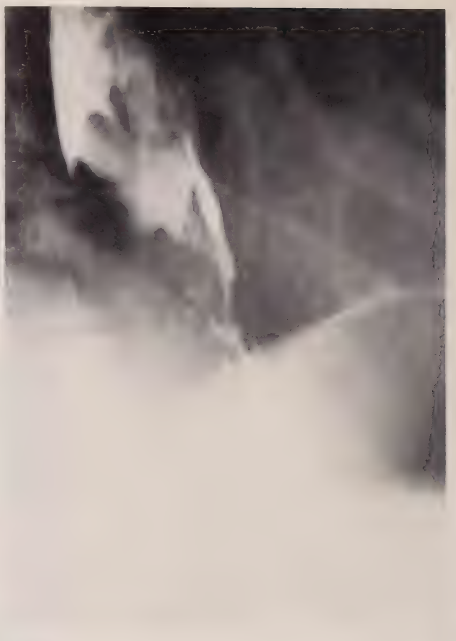


Fig. 5. **Left** White man, age 69, with chronic myelogenous leukemia. Esophagram shows typical inflammatory changes of candidiasis.

Fig. 6. **Right** White woman, age 26, with acute myeloblastic leukemia. Esophagram performed because of sudden difficulty swallowing shows foreign material completely obstructing distal esophagus which at endoscopy proved to be candidiasis plus sloughed, necrotic esophageal mucosa.

branous enterocolitis is most often diagnosed clinically, it usually shows bowel distention on plain radiographs; typical plaques and ulcerations are frequently present on barium studies. The rare case of pneumatosis intestinalis is diagnosed by either plain films or barium examination. Vincristine megacolon and other related problems are diagnosed by plain radiographs or barium studies.

Typhlitis should be especially looked for in children with acute myelogenous leukemia (11). Its radiographic appearance is variable. There can be plain radiographic and barium enema findings of cecal and ileal mass effect and bowel edema ("thumb-printing") or a paucity of gas in the right lower quadrant, with slight distention of the adjacent small bowel (11). Ulceration and overt necrosis with perforation and abscess formation can also be seen (Fig. 2).

Henoch-Schönlein purpura and hemolytic uremic syndrome can produce similar findings of mass effect and bowel edema; however, known leukemia and the presence of a neutropenic state would strongly support the diagnosis of typhlitis (11). Acute appendicitis and diverticular inflammation can resemble typhlitis clinically and radiographically. Uncomplicated typhlitis may be managed conservatively, but any evidence of perforation, abscess formation, or significant bleeding is an indication for surgery (11).

Summary

Early diagnosis and treatment are essential for patient survival when significant gastrointes-

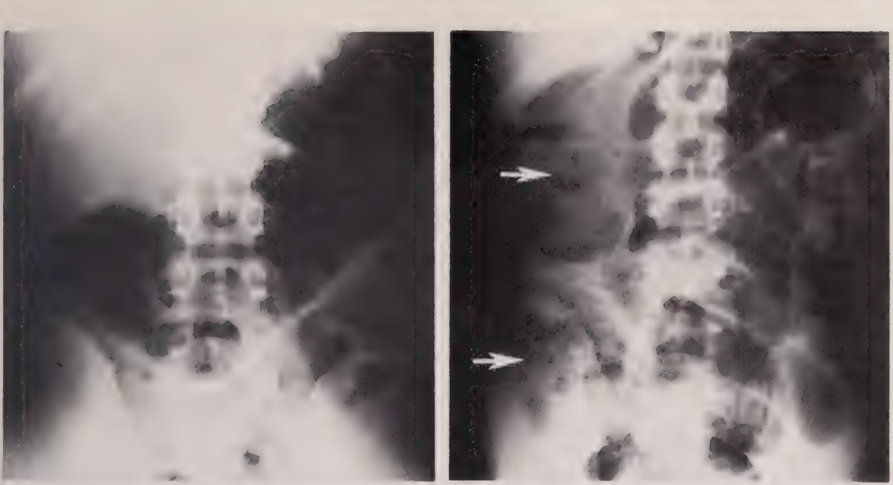


Fig. 7. White man, age 19, with acute myelomyelocytic leukemia and persistent fever. **Left** Plain abdominal film shows markedly distended colon suggestive of toxic megacolon. **Right** One day later, colon remains distended and abscess formation is present in right side of abdomen (arrows).

tinal complications of leukemia develop (7). Indications for surgery are the same for the leukemic patient as for the nonleukemic. (7) Prompt recognition of severe gastrointestinal disease via clinical, laboratory, and radiographic means enhances patient survival and well-being.

Aggressive medical or surgical therapy will often restore normal health. Almost two thirds of our patients survived their complications, and those who succumbed to their disease benefitted from significant palliation. Therefore, these complications should no longer be considered preterminal.

Acknowledgments

Dr. John Hutter provided much of the pediatric case material and Cole Thies produced the computer survey of patients used for this report. Janet Wallace and Tina Garcia typed the many revisions of the manuscript.

Figs. 1–4, 6, 7 and Tables 2 and 3 are reprinted, with permission, from AJR 1984; 142:513–518.

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Radiologic Evaluation of the Portal System by the Newer Modalities of Computed Tomography and Ultrasound

Francis F. Ruzicka, M.D.

For centuries, the portal venous system was an enigma to clinicians. Postmortem studies traditionally ignored the portal system in large part, and, at surgery, much of the portal system is difficult to evaluate under ordinary circumstances. Beginning in 1945, however, when Whipple (1) and Blakemore and Lord (2) reported on the first portal venogram, many of the mysteries of the portal system have gradually been unraveled (with major contributions to understanding of the liver), concurrent with the improvement in radiologic techniques. Following operative portal venography, there came splenoportography, then umbilical portography, to be followed by arterial portography, and then transhepatic portal venography.

The basic information derived from angiographic studies has enabled us to readily evaluate the pathologic changes that occur in the portal system as viewed by the newer radiologic approaches of computed tomography (CT) and ultrasound, in which—rather than the customary longitudinal two-dimensional image—we obtain tomographic or tomographic-like images in various planes, that is, cross-sectional, sagittal, coronal, and oblique sections. Further, both newer modalities provide, in one examination, information on the liver which can be quite helpful in overall evaluation of the presenting problem.

Basic Anatomy, Pathology, and Pathophysiology

Portal venography visualizes radiographically the portal venous system. Depending on the site of injection (Fig. 1) and the technique employed (3, 4), one can flush the system to delineate the anatomy and pathology (transhepatic portography), or one can inject into the stream of blood flow (for example, arterial portography or splenoportography) to evaluate the anatomic-pathophysiologic changes that have occurred. In the normal physiologic state, blood flow is hepatopetal; that is, it is toward the liver from every point in the portal system. However, when obstruction occurs, whether it be intrahepatic, suprahepatic, or extrahepatic, the normal large portal blood flow (1,500 ml/min) into the liver cannot be maintained and portal venous blood must return to the heart via collateral routes. Hepatofugal blood flow then occurs retrogradely over either the normal tributaries (coronary-gastroesophageal-azygous system, inferior mesenteric hemorrhoidal system, or retroperitoneal communications between the mesentery and tributaries of lumbar veins) or over certain vessels ordinarily not seen as normal tributaries of the portal system but which exist as embryonic remnants. These embryonic channels become dilated or possibly recanalized to carry blood back to the systemic system (Fig. 2).

In clinical practice, one usually encounters intrahepatic or extrahepatic obstruction. Suprahepatic obstruction, for example Budd-Chiari syndrome, constrictive pericarditis, is less common. Intrahepatic obstruction is often due to cirrhosis. In addition to cirrhosis, however, a variety of conditions, both intrahepatic and extrahepatic, may lead to the development of portal hypertension, as described by Sherlock (5). Extrahepatic obstruction may occur either at the portal vein or the splenic vein. Portal vein obstructions may be due to masses in the porta hepatis, or to carci-

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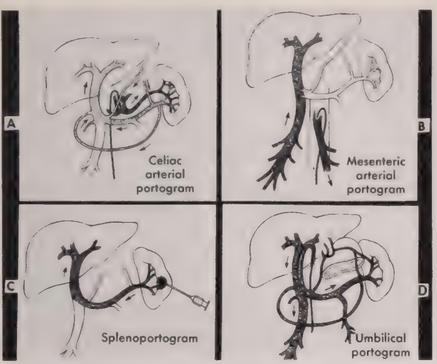


Fig. 1. Various flow patterns of blood/contrast in normal portal system depending on site of injection. Stippled vessels indicate course of contrast flow. **A** Celiac artery injection, catheter in celiac artery. Contrast medium following blood flow distributed to territories supplied by each branch of celiac artery. Large amount of blood/contrast passing over splenic artery returns to visualize splenic and portal veins. Other veins draining territories supplied are less densely opacified. Flow is hepatopetal. A selective splenic artery injection provides even better visualization of splenic and portal veins, since loss of contrast over other arterial branches is largely eliminated. Arrows indicate direction of flow in arteries and veins. **B** Superior mesenteric artery injection. Contrast visualizes only vessels between site of injection and liver, that is, flow is hepatopetal. **C** Splenic pulp injection, splenoportogram. Contrast medium carried directly from site of injection over splenic and portal veins to liver. **D** Transumbilical portogram. Same as percutaneous transhepatic portogram in which catheter tip is placed directly into selected vein of portal system. Demonstrates pathologic anatomy rather than pathophysiology.

noma of the liver or of the head of the pancreas. In about 10% of cirrhotics, bland thrombosis of the portal vein occurs.

Portal vein obstruction may also occur secondary to tumor invasion. In children, neonatal umbilical sepsis is a cause, presumably occurring in the newborn but often not manifested by gastrointestinal bleeding until later in life. Congenital abnormalities of the portal vein producing obstruction also occur. Trauma as a cause of thrombosis is sometimes encountered. Pancreatitis and retroperitoneal fibrosis are other causes of portal vein obstruction. Splenic vein obstruction may be due to similar causes, especially pancreatitis and carcinoma of the pancreas.

Ultrasonography and CT

With the extensive application of the modalities of CT and ultrasonography to abdominal problems in recent years, the portal system has been successfully visualized by both techniques. However, the cross-sectional or other plane section of imaging can present problems in interpretation when only portions of the portal system appear in the image. This becomes more difficult when the physician does not suspect that the patient has portal venous obstruction but abnormalities of the system do occur. One sees these vessels in segments in different slices, that is, cross-sectional with CT (Fig. 3) or in various planes with ultrasonography (Fig. 4). Reformatting techniques with CT can be carried out, but must be technically planned for in advance so that the appropriate cross-sectional slices can be made for suitable reconstitution in coronal, sagittal, or oblique planes. Nevertheless, in spite of the problems in both CT and ultrasound, the various segments of the portal system have been successfully used as landmarks for identification of various organs—for example, the pancreas (6–8). In addition, both modalities have been used to identify abnormalities of the portal system itself (9–11).

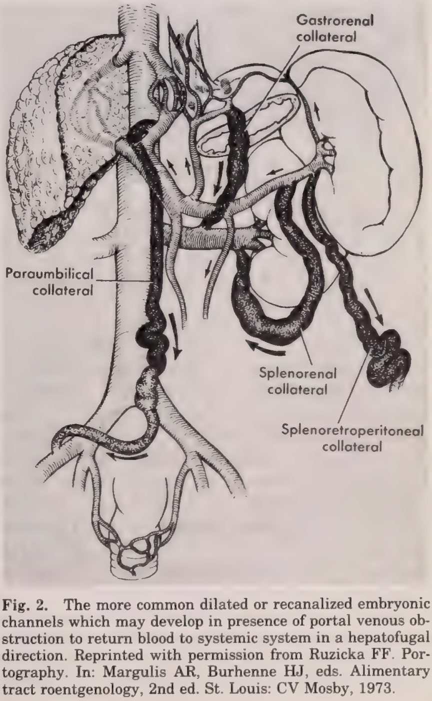


Fig. 2. The more common dilated or recanalized embryonic channels which may develop in presence of portal venous obstruction to return blood to systemic system in a hepatofugal direction. Reprinted with permission from Ruzicka FF. Portography. In: Margulis AR, Burhenne HJ, eds. Alimentary tract roentgenology, 2nd ed. St. Louis: CV Mosby, 1973.

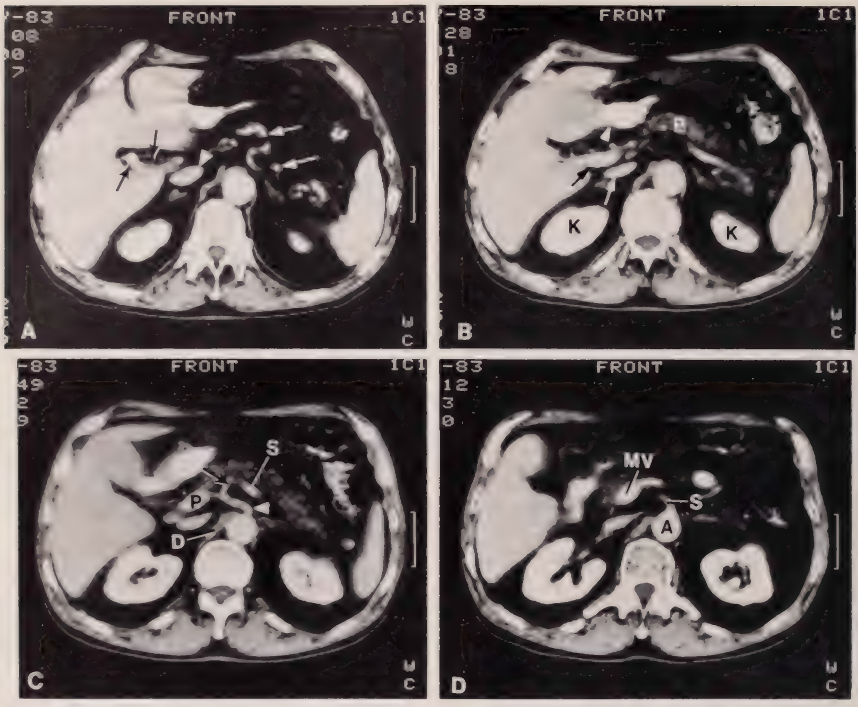


Fig. 3. Segments of portal system as seen on computed tomography following IV contrast agent. A Tortuous splenic artery (white arrows), cava (arrowhead), porta hepatis, and right portal vein branch (black arrows). B Scan 1 cm below A. Section still at level of porta hepatis. Proximity of cava to portal vein near its bifurcation (arrows). Splenic vein posterior to body/tail of pancreas. Antrum of stomach (arrowhead). Kidneys (K), pancreas (P). C Scan 1 cm below B. Celiac artery (arrowhead) and splenic artery (arrow). Main portal vein (P) remains in close proximity to cava. More proximal splenic vein (S). Racemose pattern of normal pancreas visible. Crus of right diaphragm (D). D Origin of superior mesenteric artery (S). Proximal end of superior mesenteric vein at junction with splenic vein (MV). Aorta (A).

Various associated changes in the liver may occur with cirrhosis. Fatty degeneration is readily recognizable by CT. It may be diffuse or focal and shows a decrease in attenuation of the x-ray beam in the areas affected (Fig. 5C, D). Maintenance of portal architecture has been reported (12) as a feature of fatty infiltration of the liver, in contrast with space-occupying masses which may also present with a low density but in which the architecture is distorted. Similarly, ultrasound will provide evidence of fatty change in the liver by virtue of the increase in echodensity that the fat produces. Piekarski et al (13) have found a significant correlation of CT numbers between the liver and spleen in patients with normal livers. The liver and spleen CT numbers varied concordantly. Using these results, they were able to diagnose more subtle fatty infiltration in addition to other disease changes which alter liver density.

Ascites is readily recognized on both CT and ultrasonographic evaluation of the abdomen. It is restricted to the various compartments of the peritoneal cavity and has a CT attenuation coefficient lower than that of most adjacent structures (Fig. 6B). Ascites readily transmits the sound beam so that the liver and other structures are surrounded by a low echoic or anechoic space (Fig. 7A). Ascites is most often an accompaniment of neoplasm, but is not infrequently associated with cirrhosis (14). Another characteristic finding in cirrhosis is the nodular contour of the liver

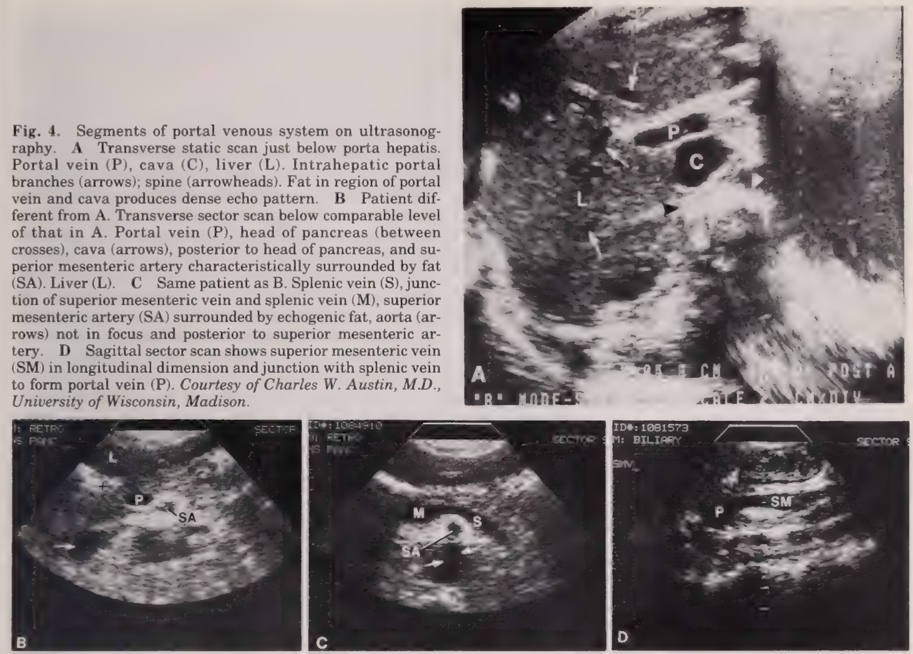


Fig. 4. Segments of portal venous system on ultrasonography. **A** Transverse static scan just below porta hepatis. Portal vein (P), cava (C), liver (L). Intrahepatic portal branches (arrows); spine (arrowheads). Fat in region of portal vein and cava produces dense echo pattern. **B** Patient different from A. Transverse sector scan below comparable level of that in A. Portal vein (P), head of pancreas (between crosses), cava (arrows), posterior to head of pancreas, and superior mesenteric artery characteristically surrounded by fat (SA). Liver (L). **C** Same patient as B. Splenic vein (S), junction of superior mesenteric vein and splenic vein (M), superior mesenteric artery (SA) surrounded by echogenic fat, aorta (arrows) not in focus and posterior to superior mesenteric artery. **D** Sagittal sector scan shows superior mesenteric vein (SM) in longitudinal dimension and junction with splenic vein to form portal vein (P). *Courtesy of Charles W. Austin, M.D., University of Wisconsin, Madison.*

(Figs. 5A, 7). In advanced cirrhosis, the right lobe of the liver is likely to diminish in size, contracting with the extensive fibrotic process, whereas the caudate lobe (Fig. 5A) and the left lobe frequently increase in size. These findings of ascites and liver configuration are readily demonstrated by both CT and ultrasound. The association of the deformed nodular liver with caudate lobe hypertrophy and ascites makes the diagnosis of cirrhosis with portal hypotension highly probable.

Ultrasonography. With ultrasonography, the portal vein, the main intrahepatic portal branches, the splenic vein, and the superior mesenteric vein can usually be identified (Fig. 4). Ordinarily, these vessels are more important as anatomic landmarks than as aids in the discovery of an abnormality of the portal system. However, ultrasonography can be used specifically to evaluate the portal system itself. Kane and Katz (9) have effectively demonstrated a variety of pathologic alterations of the portal system employing real-time ultrasonography. These include a large dilated inferior mesenteric vein, gastric varices along the lesser curvature and greater curvature of the stomach, varices of the gastroesophageal junction, echogenic tumor thrombus filling the lumen of the portal vein, and multiple tortuous collaterals in the porta hepatis with absence of portal vein, indicating complete obliteration of the portal vein. Others (10) have shown large portal system collaterals including dilated coronary vein, umbilical vein, and splenorenal shunt.

Studies indicate that, although the size of the portal vein is not a strictly reliable indication for portal hypertension, nevertheless a lack of normal caliber variation (an increase during inspiration and decrease during expiration) in the portal, splenic, and superior mesenteric veins is a good measure for portal hypertension (15). The latter is reported to show a sensitivity of 79.7% and specificity of 100%. When sensitivity was based on dilatation of the portal vein alone, the figure dropped to 41.8%. The Doppler technique can provide information on blood flow in the portal vein which can be useful in assessing whether there is increased or decreased flow to the liver.

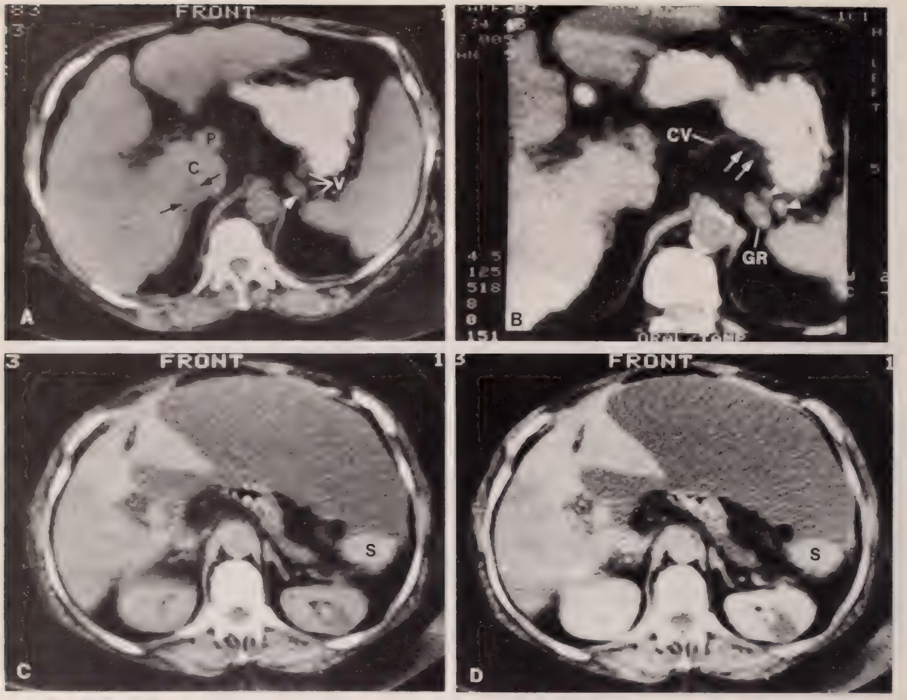


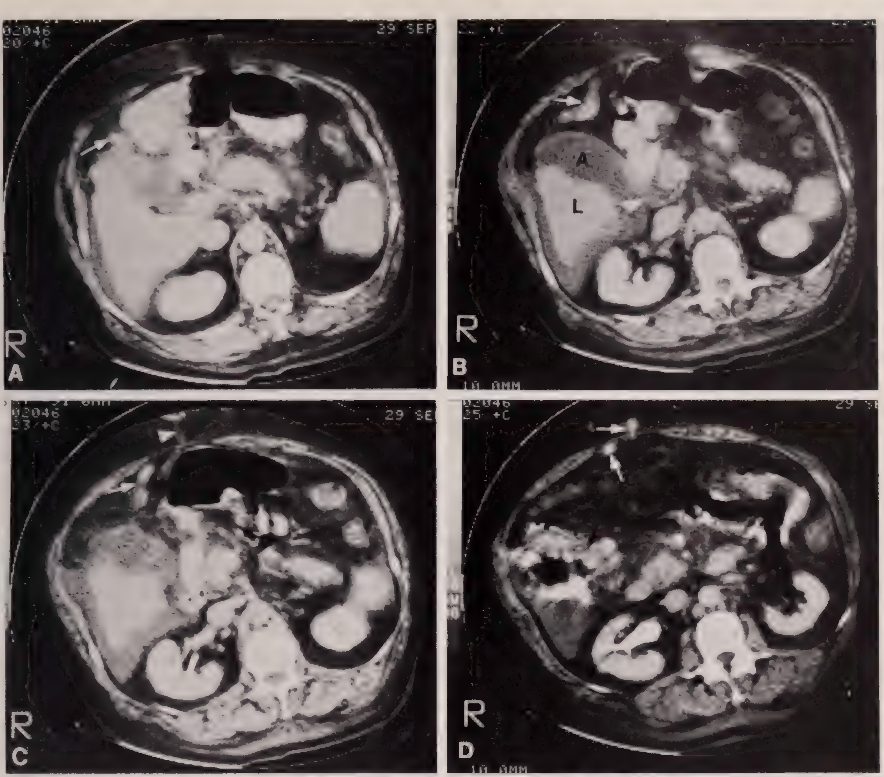
Fig. 5. A Nodular liver in cirrhotic patient. Enlargement of caudate lobe (C) and splenomegaly; portal vein (P); retrogastric varices (V); cava within caudate lobe (arrows); beginning of gastrorenal collateral (arrowhead). (See course of gastrorenal collateral in Fig. 10, same patient.) B Submucosal varices (arrows); perigastric varices (arrowheads); gastrorenal collateral (GR); coronary vein (CV). Stomach filled with gastrografin. C Fatty degeneration of liver indicated by patchy attenuation of most of right lobe. D After intravenous contrast, fatty change in liver is better appreciated. Large collection of fluid to left and anteriorly appears to be loculated and displaces liver to right and stomach posteriorly.

Dach and collaborators (16) have reported a study of sonographic evaluation of portal hypertension in 16 patients who had bleeding gastroesophageal varices. The sonogram demonstrated anechoic venous structures at characteristic sites, that is, in the region of the lower esophagus, the cardia, and the lesser curvature of the stomach. Of ten patients with coronary vein visualization by arterial portography, in nine the coronary vein was seen with ultrasound examination. All 16 of these patients had endoscopic proof of gastroesophageal varices, and 12 had varices shown by angiography. Of these 12, ten had sonographic evidence of varices at the gastroesophageal junction and along the lesser curvature of stomach.

The sonographically patent and dilated umbilical vein has been reported as a sign of portal hypertension (Fig. 6E). In a study by Saddekuri et al (17), the authors concluded that a patent umbilical vein is a diagnostic sign of portal hypertension, provided that the lumen of the vein is greater than 3 mm in diameter and that it extends a considerable distance away from the left portal vein branch from which it arises and is seen within the falciform ligament.

A study (Folia Morphol 1976;35:173–179) by Warsz quoted by Saddekuri et al (17) of 200 corrosion specimens of the portal system showed the lumen of the umbilical vein to be patent in adults up to 16 cm from its junction with the left portal vein. The mean diameter of this vessel was 2.3 mm.

The "bull's-eye" falciform ligament sign is a sonographic finding of portal hypertension (18). This is produced by the dilated umbilical vein which, under the influence of obstruction, en-



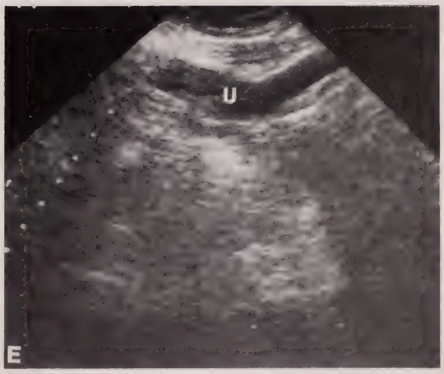


Fig. 6. **A** Dilated umbilical vein in cirrhotic patient with portal hypertension. Umbilical vein (arrow) emerging from anterior aspect of falciform ligament. **B** Section made 2 cm below A. Umbilical vein (arrow) present in extraperitoneal fat behind anterior abdominal wall. Vessel density enhanced by IV contrast. Ascitic fluid (A) within peritoneal cavity about right lobe of liver (L). **C** CT section 1 cm below B. Umbilical vein (arrow) extending toward region of umbilicus. Umbilicus (arrowhead). **D** CT section 2 cm below C. Umbilical vein (arrow) passing through abdominal wall. Below this, it will join superficial epigastric vein. **E** Transverse ultrasound sector scan showing dilated umbilical vein (U) extending from right toward umbilical region. Umbilical vein corresponds to position of vessel seen in C.

larges and can be seen as an anechoic area within the echodense fat of the falciform ligament. The ligamentum teres is itself not normally visible. In the series of 29 patients with cirrhosis reported by Schabel et al (18), a recanalized umbilical vein was seen in five. This is about the incidence of dilated umbilical veins that might be expected in cirrhotics with portal hypertension.

In another study (19), the presence or absence of portosystemic venous collaterals in 50 patients with known portal hypertension was determined. There were 32 optimal scans that showed a sen-

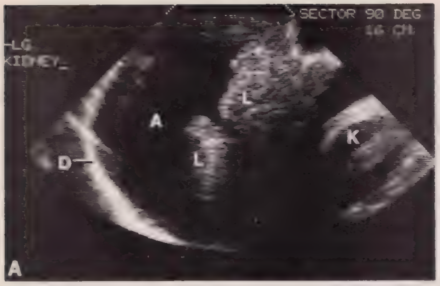


Fig. 7. Cirrhotic liver, separated from diaphragm (D) by ascites (A). Liver (L) is contracted, nodular and deformed. Kidney (K). *Courtesy of Charles W. Austin, M.D.*

sitivity for identifying at least one collateral in 88%. The sensitivity for the whole group (optimal and suboptimal scans) was 70%. The sensitivity for identifying coronary gastoresophageal collaterals specifically was 80% in the optimal scan group and 64% in the suboptimal. These investigators were able to identify the coronary vein, gastroesophageal varices, the umbilical vein, and pancreaticoduodenal varices.

Further, they were successful in visualizing splenorenal, gastrorenal, and omental collaterals. These authors concluded that the demonstration of the coronary vein within the lesser omentum and the finding of gastroesophageal varices are the most common and reliable sonographic findings in patients with portal hypertension. They define a dilated coronary vein as greater than 5 mm in diameter. Further statistics in this series indicated that in patients with large varices, the coronary vein was detected in 89% and gastroesophageal veins in 68% of patients. In patients with small varices by endoscopy, the sensitivity dropped to a detection rate for coronary vein of 63% and gastroesophageal veins for 18%. In children, the abnormal coronary gastroesophageal system can be visualized in 87% of cases (20).

Ultrasound has also been used to demonstrate portal vein thrombosis. The extrahepatic portal vein and its major tributaries as well as the splenic and superior mesenteric veins are constant vascular landmarks that are seen with a high degree of consistency in the examination of the upper quadrants. Three cases of portal vein thrombosis confirmed by angiography or surgery were demonstrated by Merritt (21). The positive findings included direct visualization of a thrombus within the lumen of the portal vein, obliteration of the normal portal venous landmarks, and secondary signs of dilatation of the splenic and mesenteric veins. In one case in which the author was able to show no major vessel of the portal system, all three vessels were occluded at surgery.

In a study of 12 children (14 months to 8 years of age), Sassoon et al (22) showed portal cavernomas with the following etiology: idiopathic, 5; omphalitis secondary to catheterization of the

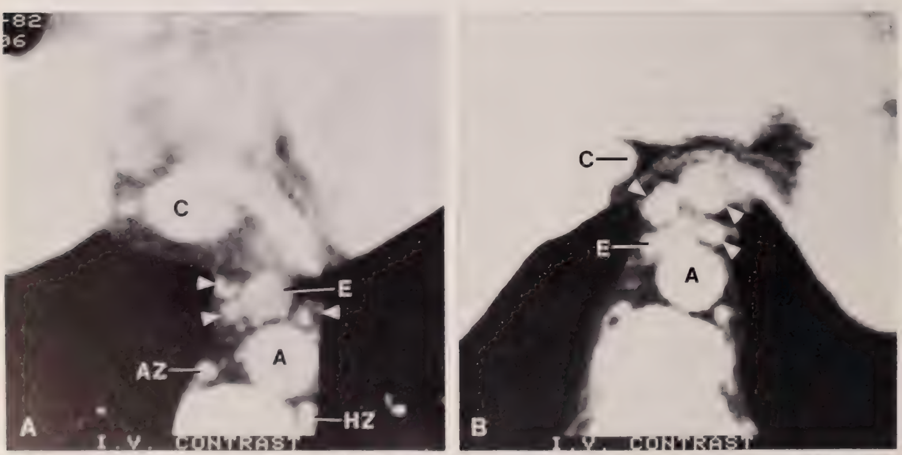


Fig. 8. A Esophageal and periesophageal varices. Note stippled pattern of opacification in esophagus (E); aorta (A); cava (C). Dilated periesophageal veins present on either side of esophagus (arrowheads). Azygos vein (AZ). Hemi-azygos (HZ). **B** Scan 2.5 cm inferior to A. Paraesophageal varices (arrowheads), esophagus (E), aorta (A).

umbilical vein in the neonatal period, 6; trauma, 1. The sonographic signs consisted of absence of the normal portal vein or its major divisions and small linear echoes dotting the portal vein or the porta hepatis area (representing bridging collaterals).

The employment of pulsed Doppler ultrasound in the evaluation of patency of splenorenal anastomoses is discussed in the section on computed tomography.

Computed Tomography. Varices in various locations are recognizable on CT (Fig. 8, 5B). In an article with excellent illustrations, Ishikawa (11) reported the demonstration of esophageal varices by CT in 18 of 25 cases that were shown to have varices by other methods. They also showed a mediastinal venous mass due to dilated azygous and periesophageal veins. Enhancement of the vessels by intravenous injection greatly facilitates the identification of these vessels. They were also able to demonstrate the gastrorenal and paraumbilical collaterals, a portal vein aneurysm, and a caput medusae.

Similarly, Clark et al (23) have visualized varices in the periesophageal, perigastric, peripancreatic, and pararenal, and gallbladder areas. They describe the use of contrast-enhanced CT to define the extrahepatic portal system and to differentiate varices from lymphadenopathy and soft tissue tumors.

Because of the frequent use of the enhancement technique, that is, the use of intravenous contrast to better visualize vessels in the abdominal cavity, it has become commonplace to identify the various venous structures, especially the vena cava, the renal veins, the splenic vein, the superior mesenteric vein, and the portal vein. Pasani et al (24) carried out a study in which they used 300cc of 30% contrast agent in a pedal vein (some patients receiving an additional bolus of 75 to 100 ml of 60% contrast over 25 seconds). They show examples of a thrombosed vena cava with collateral ascending lumbar veins, short gastric veins in the presence of splenic vein obstruction secondary to carcinoma of the pancreas, and obliteration of the normal perirectal fat plane due to collaterals of the middle and inferior hemorrhoidal plexuses secondary to obstruction of the cava.

One of the problems encountered in CT examination of the abdomen is the differentiation of masses (both primary tumors and enlarged lymph nodes) from either normal structures such as nonopacified bowel loops or from dilated and tortuous vessels. Gould et al (25) reported on the problems encountered in distinguishing dilated varices and collateral veins that may be found in portal hypertension from retroperitoneal masses. They show huge vessels of a mesocaval shunt, producing a large mass anterior to the right kidney in one patient (Fig. 9), a suspected left adrenal mass that was shown to be due to huge paragastric varices in a second patient, and, in a third patient, a lobular left retroperitoneal mass anterior to the left kidney and psoas muscle which was shown on angiography to be a large splenorenal collateral.

The importance of differentiating vessels from masses becomes critical when one is studying a patient who has a known lymphoma or in whom a search for metastatic disease is being carried out. All masses that enhance do not represent dilated vessels. Some inflammatory and neoplastic masses and lymph nodes may enhance; however, given an appropriate history and location of the enhanced mass, especially when it appears tubular in structure either over several sections or in a reformatted sagittal or coronal section, portal venous obstruction with collateral vein development can be seriously considered. At other times, the history together with the findings on CT can be so specific that no further study is needed as far as the diagnosis of portal hypertension is concerned. If surgery is to be performed, however, it is always necessary to delineate the venous structures by angiography for surgical planning.

Foley et al (26) have described the use of dynamic CT and duplex ultrasonography as adjuncts to arterial portography in demonstrating that the splenic or portal vein is patent when the conventional celiac arteriogram, or even the selective splenic arteriogram and superior mesenteric artery injection, fails to show the splenic vein during the venous phase of the study because of splenomegaly and consequent dilution by the large volume of blood in the spleen, or because of predominant flow patterns in the portal system carrying contrast away from the splenic-portal axis.

Computed tomography, because of its limited area of coverage by cross-sectional imaging, may have considerable difficulty in demonstrating a specific vein that extends through more than one plane, either because of position or tortuosity. But repeated boluses of contrast with scans at selected levels often are successful in bringing out the vein that is being investigated. By coronal and sagittal reformatting, it is often possible to demonstrate these vessels in another dimension. Real-time/pulsed Doppler ultrasonography (re-

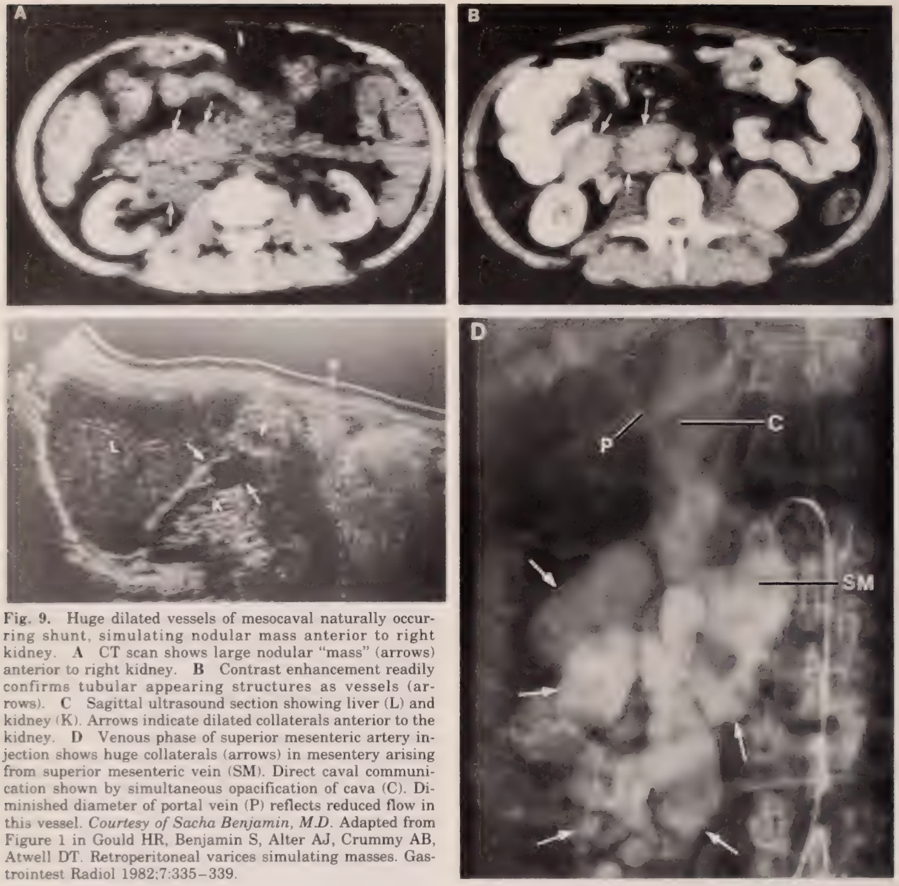


Fig. 9. Huge dilated vessels of mesocaval naturally occurring shunt, simulating nodular mass anterior to right kidney. **A** CT scan shows large nodular "mass" (arrows) anterior to right kidney. **B** Contrast enhancement readily confirms tubular appearing structures as vessels (arrows). **C** Sagittal ultrasound section showing liver (L) and kidney (K). Arrows indicate dilated collaterals anterior to the kidney. **D** Venous phase of superior mesenteric artery injection shows huge collaterals (arrows) in mesentery arising from superior mesenteric vein (SM). Direct caval communication shown by simultaneous opacification of cava (C). Diminished diameter of portal vein (P) reflects reduced flow in this vessel. *Courtesy of Sacha Benjamin, M.D.* Adapted from Figure 1 in Gould HR, Benjamin S, Alter AJ, Crummy AB, Atwell DT. Retroperitoneal varices simulating masses. Gastrointest Radiol 1982;7:335–339.

cording the Doppler signal and image at the same time) can be used complementary to dynamic CT for determination of flow direction, vessel patency, and dynamics at specific selected sites. The segments of the portal system that are accessible to ultrasound are the proximal splenic vein, the portal vein, and the hepatic veins.

For dynamic CT studies used to evaluate splenorenal shunt patency, the following technique has been employed by Foley et al (27): (a) A series of contiguous level noncontrast scans are made to extend between the splenic hilum and renal hilum from a localization digital radiograph. (b) Single-level dynamic scanning at the level of the shunt site following an intravenous bolus of 40 ml of 60% Renografin at a rate of 8 cc/sec is carried out using an automatic injector. (c) Six 4.8 second scans, each 1 cm thick, are made within 36 seconds. (d) Scanning begins ten seconds after the start of injection. (e) Following this, a sequence of contiguous incremental scans during delivery of 80 to 100 ml of additional intravenous contrast is made between the left renal hilum and the splenic hilum. Each scan is 4.8 seconds, with a four second delay between scans. By using this technique, the authors were able to demonstrate the anastomotic site of a splenorenal anastomosis in all cases. Coincident increase in density of distal splenic and renal veins was an accurate predictor of shunt patency.

Summary

At the present time, CT and ultrasonography do not provide the same completeness of visualization of the portal system that angiography offers, that is, a fully delineated, longitudinal, two-dimensional image. But varices (Figs. 5A,B; 8) and collateral vessels (Figs. 6, 9, 10) can often be recognized. Not infrequently, the site of portal venous obstruction (Fig. 11), whether intrahepatic or extrahepatic, can be identified. With this constellation of findings, the diagnosis of portal hypertension can be made. Portal venography is mandatory if surgery is planned.

The porta hepatis and various components of the portal system can be well demonstrated by CT (Fig. 3). Generally, CT delineates the total anatomy more satisfactorily than ultrasonography because of its ability to picture all of the other regional anatomic structures in cross-section. Sonography, however, is no less precise using segmental real-time images and having the capacity to obtain images in any plane. Dynamic CT, with its rapid sequential imaging during the time of greatest concentration of contrast in the splenic and portal veins, can indicate the location of obstruction. At times, these modalities can be complementary to one another.

As already described in the foregoing paragraphs, the presence of a dilated umbilical vein can be readily detected by ultrasonography. If this vessel is larger than 3 mm, the diagnosis of intrahepatic portal obstruction and portal hypertension is likely. Figure 6 demonstrates the dilated umbilical vein by both ultrasonography and CT. Among other major collaterals that are demonstrable are the splenorenal collateral, the gastrorenal collateral (Fig. 10), and the mesocaval collateral (Fig. 9). These reconstituted embryonic channels tend to be large when they do develop, producing practically simultaneous opacification of the cava.

It is sometimes difficult to differentiate between the gastric origin and the splenic origin of the gastrorenal and the splenorenal collateral because of the close proximity of the stomach and the spleen and the meandering tortuous course these vessels are likely to take. Consequently, even sections in multiple planes can be confusing. Nevertheless, the termination of this collateral in the left renal vein can be recognized by following it to the renal vein (Fig. 10), which will be larger than usual in diameter. Similarly, the cava usually shows some increase in diameter.

Extrahepatic portal venous obstruction is demonstrable by CT or ultrasonography. In Fig. 11, bridging collaterals (so-called cavernoma) indicating obliteration of the portal vein are seen well both before and after the IV injection of contrast agent. The latter developed in a patient who had abdominal trauma requiring splenectomy and 80% pancreatectomy.

Gastroesophageal varices are readily demonstrable by both ultrasound and CT. The ability to direct the sonic beam in any direction is an advantage in ultrasonography. The accuracy of ultrasound is reasonably good in the detection of varices. As stated above, large varices are detectable in 68% of patients, and the detection of a large coronary vein is achievable in 89%. Ishikawa (11), again as described above, was able to show esophageal varices by CT in 18 of 25 cases (72%). Clearly, duodenal, mesenteric, cecal, and sigmoidal varices would be more readily demonstrated by CT which visualizes these areas of the abdominal cavity more effectively and more completely than ultrasound.

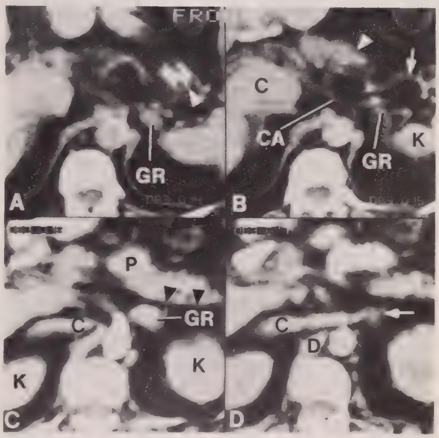
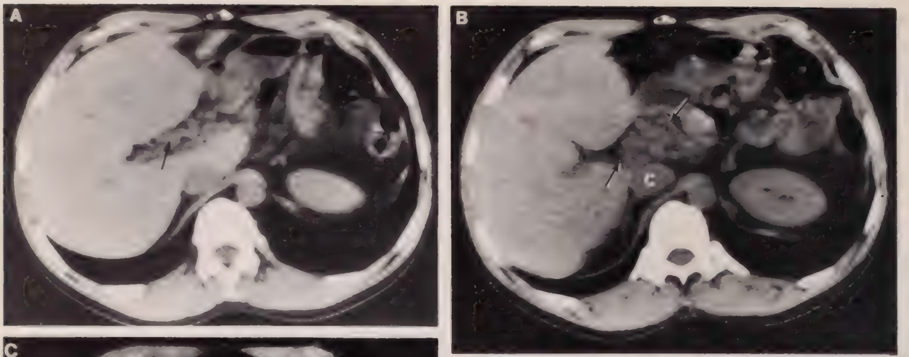


Fig. 10. Gastrorenal collateral. Same patient as Fig. 5A, B. **A** Gastrorenal collateral (GR) near origin from stomach. Gastrografin in fundus (arrowhead). Multiple small veins between gastrorenal collateral and fundus. **B** Gastrorenal collateral (GR) 1 cm below A. Body of pancreas (arrowhead). Splenic vein near hilum of spleen (arrow). Caudate lobe (C). Celiac artery (CA). **C** Gastrorenal collateral (GR). Pancreas (P). Splenic vein (arrowhead). Kidneys (K). Cava (C). **D** Junction of gastrorenal collateral with left renal vein (arrow) which crosses anterior to aorta to cava. Crus of diaphragm (D). Cava (C).



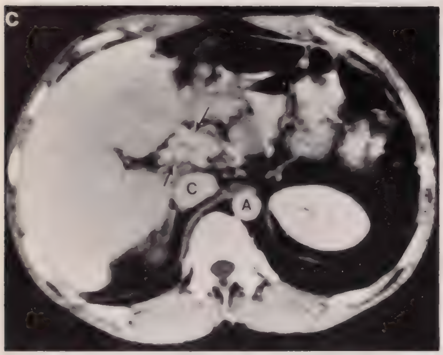


Fig. 11. 34-year-old male with history of motor vehicle accident, splenectomy, and 80% pancreatectomy three years prior to this examination. **A** Tortuous dilated vessels in porta hepatis, seen well even before administration of contrast agent (arrow). **B** Scan 1 cm below A, again without intravenous contrast, shows tortuous collaterals that bridge obstructed portal vein. Cava (C). **C** Dynamic computed tomography. After bolus injection IV contrast, bridging collaterals forming a pseudo-cavernoma (arrows) become opacified in region of porta hepatis. Cava (C). Aorta (A).

Endoscopic detection of esophageal and gastric varices remains the most accurate method without question. Nevertheless, investigation for varices by ultrasound or CT is indicated, depending on other additional clinical problems that might also require study by ultrasound or CT. Furthermore, a discovery of varices as a fortuitous and unsuspected finding does occur from time to time, and recognition of these varices by either modality is important (Fig. 9). Dynamic CT, as described by Foley et al, can be useful in evaluating the patency of splenorenal shunts.

Whether it is the portal system that is the object of study, or the pancreas or some other upper quadrant problem, ultrasound and CT give considerable additional information that portal venography and endoscopy do not. Thus, the fatty liver is important to recognize, and the diagnosis can be made by either method. Either method gives details of the pancreas, whether the problem is carcinoma or pancreatitis, which are usually not achievable by the other methods. Upper quadrant masses and aggregates of lymph nodes are readily identified by both methods—often better with CT if they are retroperitoneal. The choice of ultrasonography or CT will depend on the working diagnosis, habitus of the patient, and presence or absence of gas in the bowel. But whichever modality is selected, the information derived regarding both the basic disease and the abnormalities of the portal system will often outweigh that obtainable from other modalities. Further, ultrasound and CT are not mutually exclusive; they may very well be complementary methods.

This subject should not be closed without a few words on nuclear magnetic resonance (NMR) imaging of the liver and portal system. It is already obvious that this new modality, although still in technological and clinical infancy, will play an important role in studies of the liver and portal system. Higgins et al (28) state that because of the high contrast between flowing blood (which in most situations produces little or no NMR signal) and adjacent structures, vessels are usually well delineated without the use of contrast media.

The relationship of venous structures within the liver and porta hepatis are very well shown. Similarly, the superior mesenteric vein, splenic vein, and confluence of these veins to form the portal vein are readily demonstrated on sequential images. One would expect various lesions of the liver as well as portosystemic collaterals and varices to be readily demonstrated. Moreover, since direct imaging in any plane (without reformatting) is possible with NMR, questions concerning the course of tortuous vessels may be more readily clarified with the magnetic resonance modality. Further, this technology avoids the use of ionizing radiation, and at least at this point in time, the use of contrast agents. Time will determine its full role in the areas of liver disease and portal hypertension.

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A Dozen Pediatric Ultrasonic Donuts

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Abstract

This report describes those diseases of childhood which produce circumferential thickening of the wall of the bowel, resulting in a "donut" on ultrasonic scans. The cases have been selected from the files at Children's Hospital in Boston. Unlike the situation for adult patients, most diseases which cause circumferential thickening of the intestinal wall in children are benign. The diagnoses include chronic granulomatous disease, eosinophilic gastroenteritis, cystic fibrosis, peptic disease, duodenal hematoma, pyloric stenosis, idiopathic intussusception, inflammatory bowel disease, megacolon, and lymphoma.

Ultrasonographers have viewed the gastrointestinal tract primarily with annoyance. Its intraluminal gas often thwarts attempts at scanning pancreas and other retroperitoneal structures. Its solid or liquid contents produce pseudomasses; loops of small bowel filled with fluid can be difficult to differentiate from abscess; and the colon filled with stool may masquerade as tumor.

Over the past few years, however, ultrasonographers have recognized the gastrointestinal tract as an inevitable presence in the abdomen and have characterized lesions associated with it. Case reports and longer papers have described, primarily in the adult, the ultrasonic appearance of a circumferential gastrointestinal mass (1–14).

This report presents the ultrasonic scans of a varied group of patients, all with pediatric problems, and all of whom had an "ultrasonic donut" representing an encircling gastrointestinal lesion. In some patients, the etiology of the gastrointestinal disease was known, the ultrasonic examination was done for other problems, and confirmation of the mass was incidental information. In other patients, the mass was identified and diagnosed by ultrasonography.

Some scans were done only on rigid-arm, grey-scale equipment. Others were done with real-time units. The slow, undulating motion of the intestines gives real-time examination an edge on delineation of abnormalities. However, because their field of view is much wider, static scans are better able to show relationships between organs. Depending on the size of the patient, a transducer of 3.5MHz, 5MHz, 6MHz, or 7.5MHz was used.

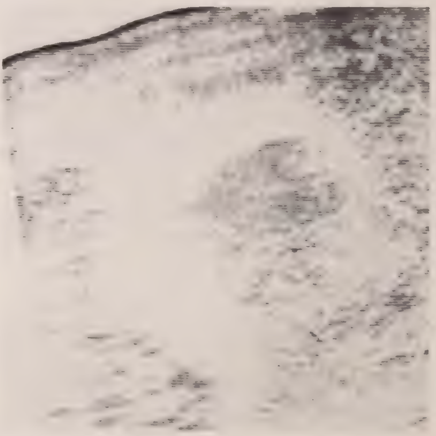

Fig. 1. Patient had been treated surgically and with chemotherapy for lymphosarcoma of terminal ileum nine years previously. New mass in right lower quadrant was an encircling gastrointestinal mass on ultrasound. Lymphosarcoma was removed at second operation.

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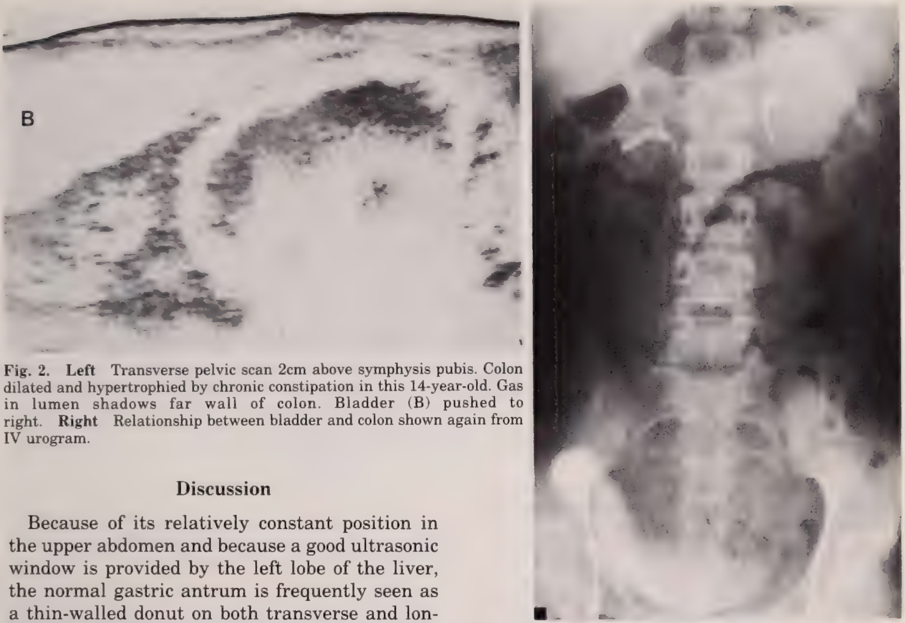

Fig. 2. Left Transverse pelvic scan 2cm above symphysis pubis. Colon dilated and hypertrophied by chronic constipation in this 14-year-old. Gas in lumen shadows far wall of colon. Bladder (B) pushed to right. **Right** Relationship between bladder and colon shown again from IV urogram.

Discussion

Because of its relatively constant position in the upper abdomen and because a good ultrasonic window is provided by the left lobe of the liver, the normal gastric antrum is frequently seen as a thin-walled donut on both transverse and longitudinal scans. Another normal donut is the gastroesophageal junction, seen to best advantage on longitudinal scans just to the left of midline. Occasionally, the rectal wall can be identified on pelvic scans, especially if rectal content is fluid.

Usually, however, an ultrasonic donut results from a pathologic process which circumferentially thickens the wall of the gastrointestinal tract. Measurements of the normal wall have been supplied in the literature. Fleischer and colleagues indicated that the normal bowel wall averaged 3mm in thickness when distended and 5mm when nondistended (15). Salem et al considered a rim >1cm in thickness abnormal (16).

The thickened wall is relatively echolucent, but the intraluminal contents, mucus and entrapped gas, are echodense (Fig. 1). Enough gas may be present to shadow the far wall of the lesion so that only half the circumference of the bowel is apparent (Fig. 2).

The diseases associated with ultrasonic donuts are antral gastritis, perforating ulcer with phlegmon, chronic granulomatous disease, eosinophilic gastroenteritis, pyloric stenosis, pancreatitis/duodenal hematoma, cystic fibrosis, Crohn's disease, intussusception, ulcerative colitis, megacolon, and lymphoma.

Most literature concerning the ultrasonic ap-

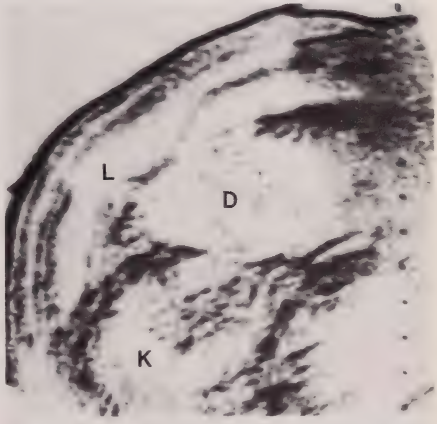

Fig. 3. Bleeding into duodenal wall and surrounding soft tissues resulted in large echolucent donut with compression of lumen. Because of previous abdominal trauma, duodenal hematoma was diagnosis. L, liver; K, kidney; D, duodenal hematoma.

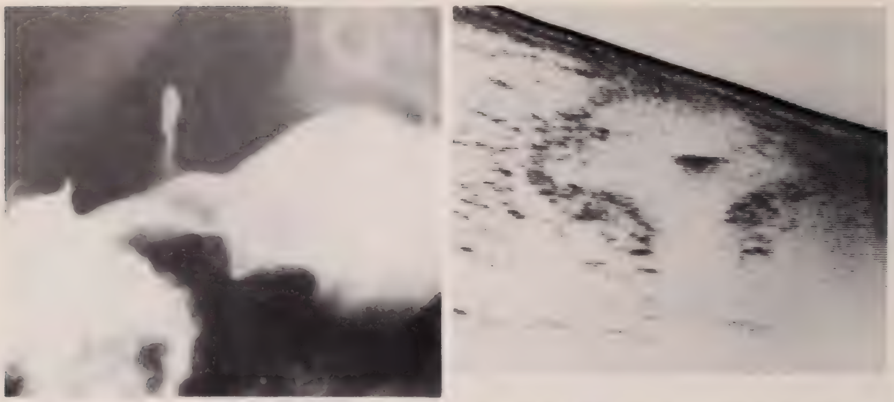

Fig. 4. Penetrating ulcer (**left**) resulted in periantral inflammation, seen as a large donut on this longitudinal scan (**right**). Possibility of ulcerating tumor was raised by size of mass but disproven by angiography and surgery.

pearance of gastrointestinal masses has been limited to diseases of adults and has described, for the most part, encircling malignant tumors. Three reports from Germany included patients with Crohn's disease and peptic ulcer disease who demonstrated *kokardenphanomen* (rosette phenomenon) on ultrasonography (1, 6, 10). Yeh and Rabinowitz reported that of 40 patients with gastric lesions, 6 had benign disease (gastritis and gastric ulcers) (17), and other large series include a few patients with benign disease (11). Sonnenberg et al directed a prospective study to identify those patients with Crohn's disease who had a "target" sign on ultrasonography (18).

Many descriptive terms have been applied to the ultrasonic appearance of a thickened bowel wall. As mentioned above, *kokardenphanomen* has been used in the German literature; "bull's-eye," "target lesion," "halo," and "pseudokidney" are terms used in the American literature.

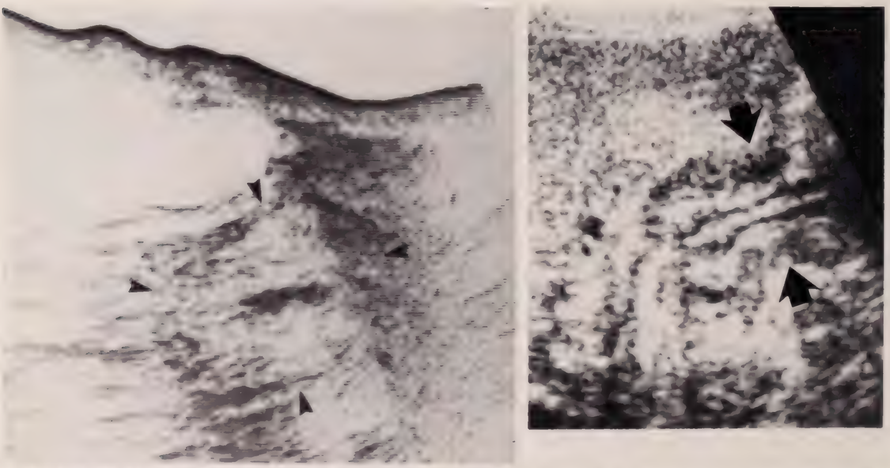

Fig. 5. **Left.** The hypertrophied pyloric muscle (arrows) is a mass with a central cleft, which represents compressed pyloric channel. **Right.** Much more detail can be seen on this real-time examination, which shows pyloric channel through hypertrophied muscle (arrows).

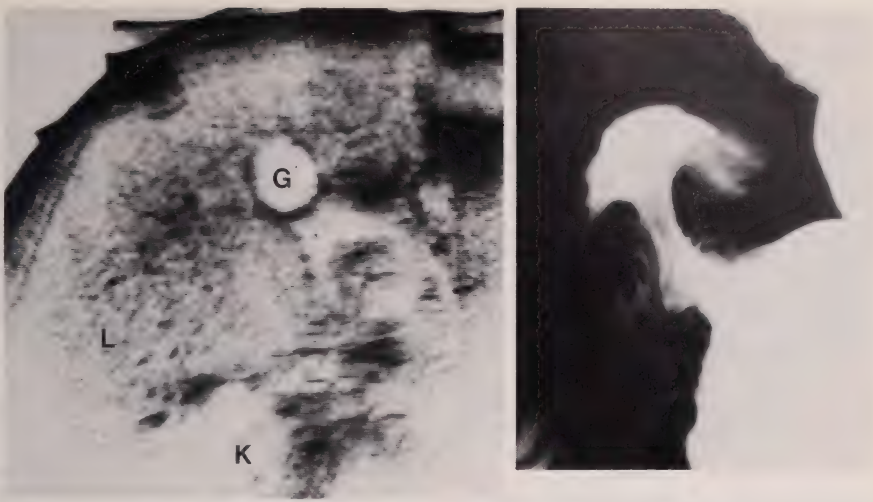

Fig. 6. A child with chronic granulomatous disease was being evaluated for possible hepatic infection. "Donut" seen adjacent to gallbladder on this transverse scan (**left**) was confirmed as granulomatous infiltration of antrum on a subsequent upper gastrointestinal series (**right**). L, liver; K, kidney; G, gallbladder.

"Donut" is less likely to be confused with other signs; "bull's-eye" is used for certain radiologic descriptions, and use of the term "pseudokidney" can be very misleading. "Donut" has obvious links to the gastrointestinal tract and is a more generic term than "bagel," although New Yorkers might disagree.

In the pediatric population, benign disease is

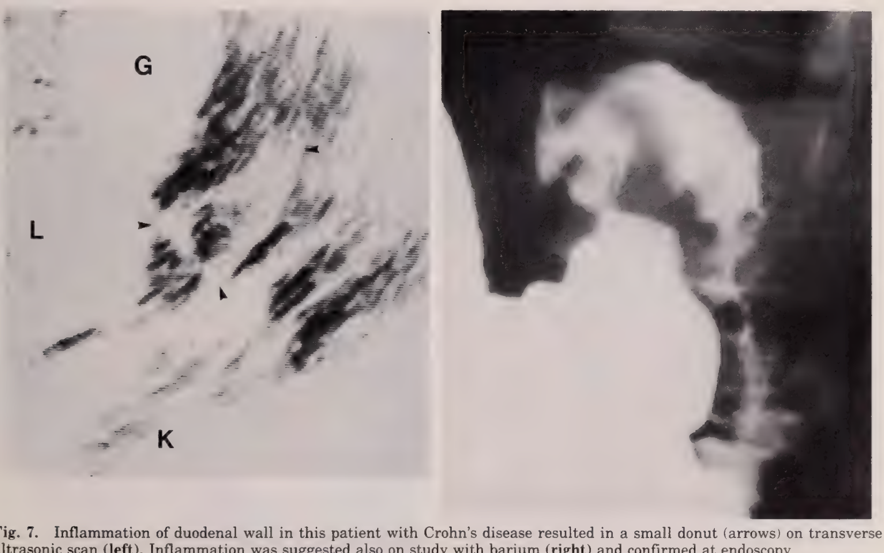

Fig. 7. Inflammation of duodenal wall in this patient with Crohn's disease resulted in a small donut (arrows) on transverse ultrasonic scan (**left**). Inflammation was suggested also on study with barium (**right**) and confirmed at endoscopy.

far more common than malignant in the group of children with ultrasonic donuts. Adenocarcinoma of the bowel rarely occurs in the young, and tumors, if present, are more likely to be lymphomatous.

Most patients with gastrointestinal lymphoma have large bulky masses (19). However, to emphasize the nonspecificity of the ultrasonic donut, children with duodenal hematoma (Fig. 3) and a boy with a penetrating duodenal ulcer (Fig. 4) had large encircling masses. One patient with lymphoma had a relatively small mass (Fig. 1).

Pyloric stenosis, resulting from idiopathic hypertrophy of the pyloric muscle in babies, is a common ultrasonic donut in children. Making the diagnosis requires careful real-time scanning in a peaceful baby whose stomach is partly distended with fluid and who is turned into partial right decubitus position (Fig. 5). Even with the availability of the most advanced equipment, the technique requires considerable practice on the part of the ultrasonographer and cooperation on the part of the baby. Several series of babies with pyloric stenosis have been reported (20–23). The thickness of hypertrophied, i.e., abnormal, muscle is generally more than 4mm.

Chronic granulomatous disease of childhood may result in antral narrowing caused by formation of granulomas in the antral wall. This thickened wall can be identified quite easily on ultrasonography (3) (Fig. 6). Crohn's disease, similarly a granulomatous process, also favors the antrum in those cases in which the stomach is involved. The patient whose scan is shown as Fig. 7 had Crohn's disease of antrum, duodenum, and terminal ileum. Usually, an ultrasonic donut is present in the right lower quadrant in children with Crohn's disease from the more common isolated ileocecal involvement.

The other unusual inflammatory disease associated with thickening of the gastric antrum is eosinophilic gastroenteritis (Fig. 8). Severe gastritis of peptic origin can cause diffuse thickening of the wall; ulcer with perforation can result in a large phlegmon (Fig. 4).

Chronic obstruction of the gastrointestinal tract leads to muscular hypertrophy of the segment of bowel proximal to the obstruction. Retention of stool in the distal colon, either secondary to Hirschsprung's disease, psychologic problems, or anatomic narrowing, produces luminal dilatation and mural thickening. (Fig. 2).

The reason for the prominent intestinal wall in patients with cystic fibrosis is still in doubt. There is no question that scans of patients with cystic fibrosis often show the gastric or duodenal wall. The wall appears slightly thicker than in normal patients, perhaps from hyperplastic Brun-

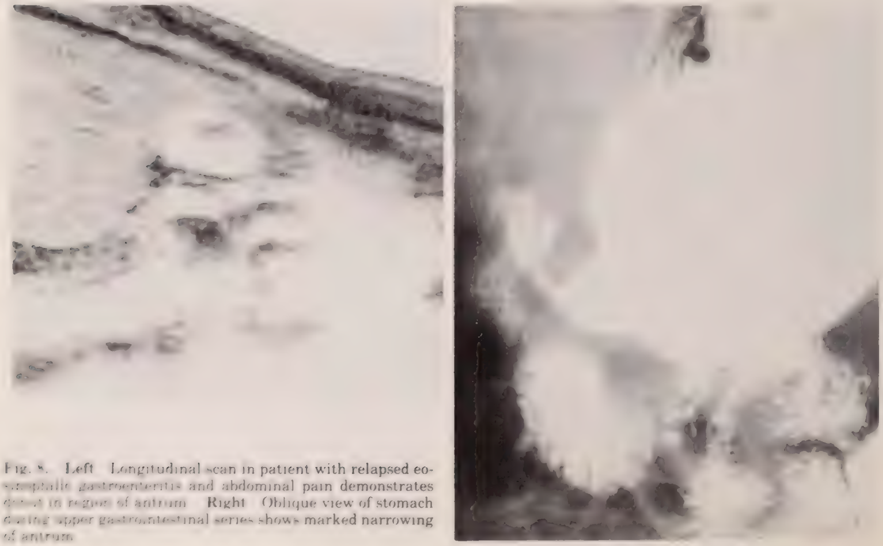

Fig. 8. Left Longitudinal scan in patient with relapsed eosinophilic gastroenteritis and abdominal pain demonstrates donut in region of antrum. Right Oblique view of stomach during upper gastrointestinal series shows marked narrowing of antrum.

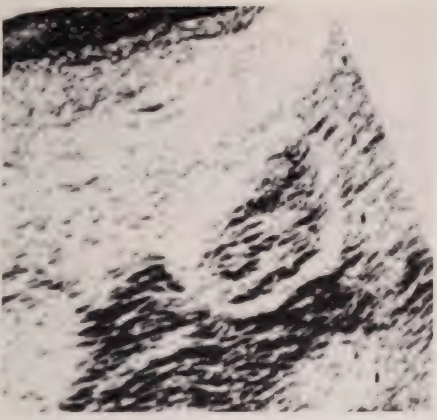

Fig. 9. Ultrasonic donut in patient with cystic fibrosis is the duodenal cap. Wall of duodenum is probably thickened by hyperplasia of Brunner's glands and accentuated by intraluminal mucous, which is more echogenic than in normal patients.

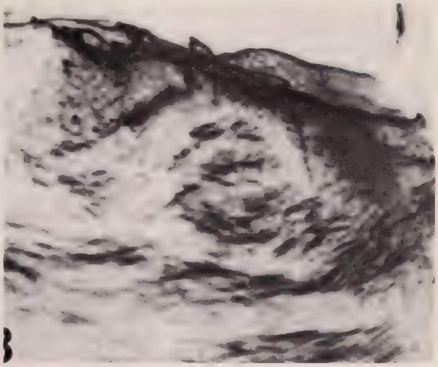

Fig. 10. Longitudinal scan, 3cm to right of midline, demonstrates "donut within a donut" configuration of ileocolic intussusception, later reduced by barium enema. L, liver.

ner's glands. In addition, it is accentuated by the intraluminal mucus which is extremely echogenic in patients with cystic fibrosis (Fig. 9) (24).

There is the special case of a donut within a donut which represents intussusception of bowel (25). In children younger than 5 years of age, intussusception is usually idiopathic, usually obvious clinically, and diagnosed and treated with contrast enema. Ultrasonography may be of use when the plain film is nondiagnostic in patients who are thought, on clinical grounds, to have intussusception (Fig. 10).

In summary: a number of diseases of childhood result in circumferential thickening of the intestinal wall. On ultrasonic scans, this thickening looks like a donut, with the central echogenicity representing intestinal lumen. Although in adults such a mass is usually malignant, benign disease accounts for the majority of donuts in children.

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Interventional Endoscopy in Diseases of the Biliary Tree and Pancreas

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Abstract

Interventional procedures for decompression of biliary tract obstruction have become part of our protocol for definitive or palliative treatment of cholestatic disorders. Endoscopic retrograde cholangiopancreatography provides access to the biliary tree and pancreas for diagnosis. Therapeutic options which are being successfully performed by experienced endoscopists include duodenoscopic sphincterotomy, peroral choledochoscopy, percutaneous T tube tract examination and extraction, balloon cholangiopancreatoplasty, and insertion of endoprostheses. Of particular significance is the technique for insertion of large-caliber endoprostheses for biliary obstruction which provides safe, effective, long-term palliation in patients with unresectable disease. Manipulation of the pancreatic duct for specific abnormalities is being performed. The current state of the rapidly developing art of endoscopic interventional techniques, indications, results, and complications is reviewed.

Endoscopic retrograde cholangiopancreatography (ERCP), a combined radiologic-endoscopic technique, has contributed significantly to the expeditious evaluation and treatment of obstructive jaundice (1–11). Since the introduction of ERCP more than a decade ago, further developments in techniques and instrumentation have established both the efficacy and safety of this procedure and its value as a diagnostic and therapeutic modality for diseases of the biliary tree and pancreas. Fig. 1, an algorithm, is a flow chart for evaluating patients with cholestasis, emphasizing the role ERCP assumes in the evaluation and management of this problem.

Because of the advantages in employing ERCP to obtain more accurate diagnoses and specific therapy, I present a brief update and review of my experience. I also review the most recent developments in this field, including endoscopic decompression of obstructive jaundice and newly evolving techniques employed in pancreatic disease. The specific interventional endoscopic procedures currently employed include ERCP, sphincterotomy, peroral choledochoscopy, percutaneous endoscopic extraction retained stones (PEERS), drains, and hydrostatic dilatation.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

I have achieved specificity of 87.9% in establishing the primary diagnosis in diseases of the biliary tree and pancreas in a series of 4,936 ERCPs (Table 1). This success is directly related to the experience of the endoscopist; as individual series increase in number, accuracy and specificity also increase (12, 13). In this large series of ERCPs, results are comparable to those obtained with percutaneous transhepatic cholangiography (PTC) in diseases of the biliary tree, even in the presence of high grade obstruction.

The low morbidity and mortality rates of ERCP offer additional advantages when these rates are compared with those of PTC (12–17). Additional advantages of ERCP include endoscopic examination for mucosal abnormalities and, most important, pancreatography, which is routinely achieved in 98% of experienced series. Early use of ERCP establishes a definitive diagnosis and, in many cases, a definitive therapy, thereby elimi-

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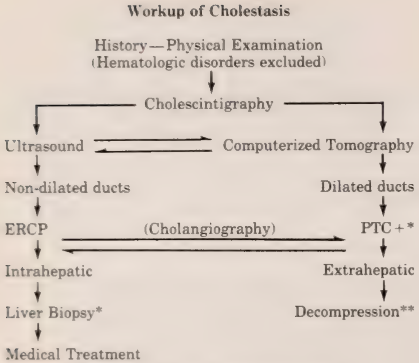
Workup of Cholestasis
History—Physical Examination
(Hematologic disorders excluded)
Cholescintigraphy
Ultrasound
Computerized Tomography
Non-dilated ducts
Dilated ducts
ERCP
(Cholangiography)
PTC +*
Intrahepatic
Extrahepatic
Liver Biopsy*
Decompression**
Medical Treatment

+ Percutaneous transhepatic cholangiography
*Normal coagulation
**Percutaneous drains*
Sphincterotomy*
Endoscopic drains
Surgery

Fig. 1. Evaluation and treatment of cholestasis.

nating both costly tertiary examinations and prolonged hospitalization (18).

TABLE 1
ERCP Specificity
(N = 4,936)

	Attempted	Cannulated (% Success)
Pancreatic disease	1,530	1,484 (97)
Biliary disease	3,406	3,236 (95)
Single duct cannulated		628
Both ducts cannulated		4,245 (86)
Total		4,873 (98.7)
Duct of intention		4,288 (87.9)

Duodenoscopic Sphincterotomy (Papillotomy)

An extension of ERCP, duodenoscopic sphincterotomy (DS) employs a catheter with a self-contained wire through which electrocautery current is transmitted (5–11). Once the wire is positioned in the bile duct, the application of electrocautery current provides a controlled incision transecting the intramural sphincter and facilitating passage or extraction of stones. The size and number of stones is not a contraindication, although stones greater than 2.5 cm require individual evaluation (Fig. 2). DS has been successfully performed in 827 cases, with a success rate of 97% (Tables 2, 3); the wordwide experience in more than 18,000 procedures has an overall rate of success of 92%. The low morbidity and mortality rates for DS in my experience (Table 4) are comparable to the experience of others (8, 9, 19).

In cholecystectomized patients with choledocholithiasis, DS is routinely performed. Data reported by Dr. E. Seifert (International Biliary Association meeting, June 1982) from European centers where DS is frequently performed in patients with intact gallbladders (approximately 40% of series) indicate its safety in this group, with subsequent cholecystectomy required in only 7.5% of patients. DS is safely performed in patients with cholangitis and septicemia and has been life saving in those patients with pancreatitis secondary to common duct stones (20). Despite increased risk factors in compromised elderly patients, the overall morbidity and mor-

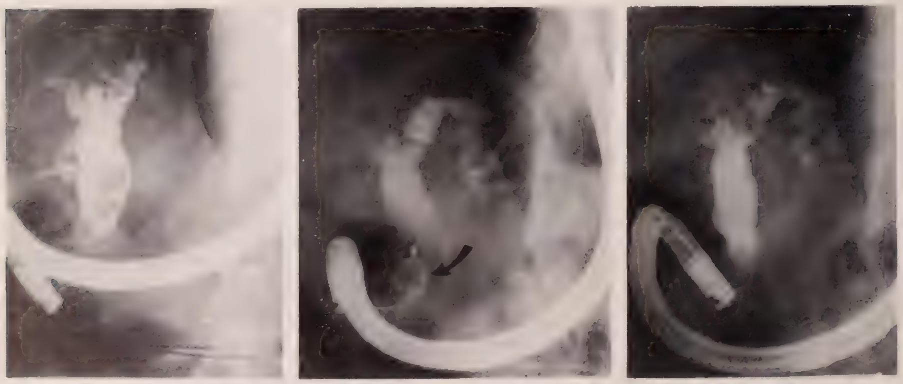

Fig. 2. Left Cholangiogram obtained at ERCP demonstrating several stones, largest measuring 2 cm in diameter; Middle Distal stones extracted after sphincterotomy. Largest stone entrapped in basket (arrow); Right Cholangiogram after all stones removed.

TABLE 2
Clinical Characteristics, Endoscopic Papillotomy
(N = 827)

Age range	26–97
Mean age	67.6
Patients over 65	628 (76%)
History cholangitis	587 (71%)
Mean hospital stay	3.8 days

tality have not been adversely affected, and the mean hospital stay remains low.

Percutaneous Endoscopic Extraction of Retained Stones

Extraction of retained stones from the bile ducts by traversing T tube sinus tracts has been effectively performed using steerable catheters and baskets (21–24). The shortcomings of this procedure, including increased exposure to x-ray and false positive findings (e.g., air bubbles), have prompted us and others (25–29) to utilize an endoscope for T tube extraction of stones. Using a bronchoscope, we were successful in 92% of attempts, comparing favorably with the catheter technique, while reducing requirements for fluoroscopy. Because direct access into the biliary tree and subsequent visualization were accomplished, false positive and negative findings were virtually eliminated.

Recently, a new choledochoscope (Olympus Corporation of America) with a diameter as small as that of the bronchoscope (4.8 mm as compared with 6.5 mm for the standard choledochoscope) has become available. This modified endoscope conforms to the configuration of a choledochoscope (rigid section with biopsy channel further down the insertion tube), but it retains the angulation of the bronchoscope, 180° up and 110° down as compared with 110° and 95° for the earlier model choledochoscope. With this newer instrument, I have employed the technique successfully in 90% of attempts (32/35). Use of this technique has reduced irradiation to both the patient and the medical team. In addition to a direct inspection of the biliary tree and extraction of stones, direct biopsies of suspected lesions offer increased diagnostic accuracy (Fig. 3).

Peroral Choledochoscopy

The sump syndrome, with its potential complications of cholangitis, cholestasis, and pancreatitis, is familiar to gastroenterologists and surgeons (30–33). However, the false positive and negative findings on cholangiography complicate the demonstration of bile duct obstruction or a

TABLE 3
Endoscopic Papillotomy
(N = 827)

	Attempted	Performed	% Success
Common duct stones	724	713	98.5
Papillary stenosis	103	94	91.3
Total	827	807	97.6

TABLE 4
Complications of Endoscopic Papillotomy
(N = 827)

Bleeding*	10	
Cholangitis, fever	13	
Pancreatitis	16	
Perforation, pain	9	
Total	48	5.8
Emergency surgery	8	0.96
Deaths	2	0.24

* Transfusions, 5.

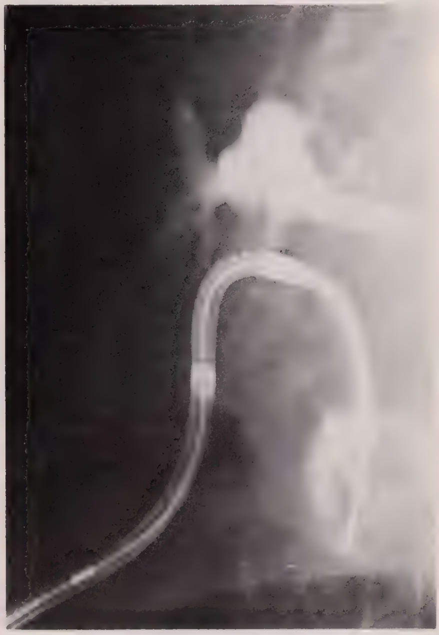

Fig. 3. Radiograph of choledochoscope advanced through T tube tract into distal common bile duct. Open biopsy forceps extends from endoscope.

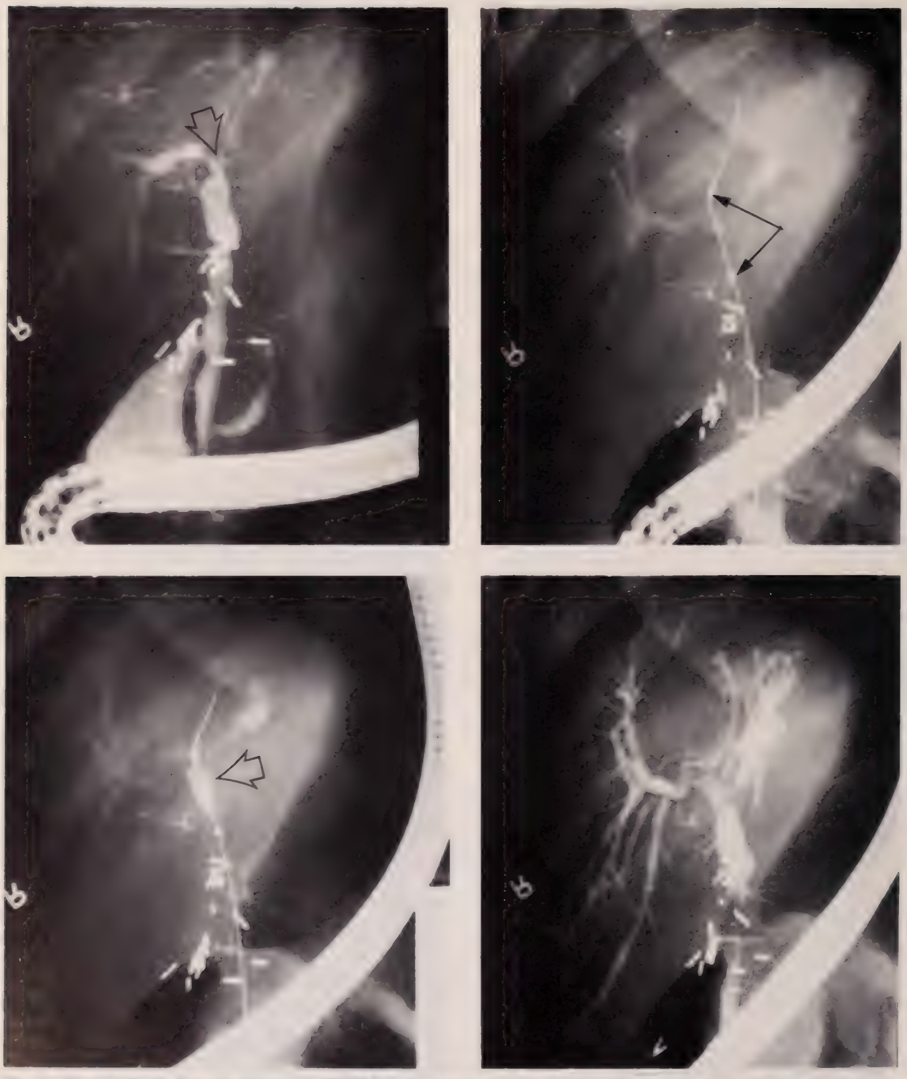

Fig. 4. **Upper left** Radiograph obtained at ERCP in patient with sclerosing cholangitis. Stricture at bifurcation of right and left hepatic ducts (arrow). **Upper right** Same patient, radiograph demonstrating wire and balloon catheter placed into stricture. Radiopaque markers in catheter define length of balloon (arrows). **Lower left** Same patient, balloon inflated (with contrast material) in stricture (arrow). **Lower right** Same patient, cholangiogram obtained after dilatation.

positive identification of filling effects. It is often difficult to demonstrate the presence of stones or debris with an enterostomy because of the presence of air bubbles from the duodenum, creating false positive filling defects on cholangiography. In cannulating either the enterostomy or the papilla of Vater, contrast material easily refluxes into the duodenum, incompletely filling the biliary tree and decreasing diagnostic accuracy.

Endoscopic examination of the bile duct may be possible when a diagnosis is uncertain. Direct examination can be carried out by the insertion of either a thin caliber or standard upper endoscope through the patent choledochoduodenostomy (34, 35). Thus, confirmation of filling defects is accomplished, and manipulation of debris or stones is possible without utilization of more invasive techniques. If the problem recurs despite a successful direct extraction, a more definitive approach using sphincterotomy or surgical revision of the enterostomy should be considered.

Endoscopic Hydrostatic Dilatation: Balloon Cholangiopancreatoplasty

Catheters with sturdy polyethylene balloons (Meditech, Inc., Watertown, Mass.) have been successfully used by the author both in diseases of the biliary tract (Fig. 4) and diseases of pancreatic duct for dilatation of benign and malignant strictures (36), and the initial short-term results have been encouraging (Table 5). The balloon measures 2 cm in length and distends to 6 mm in diameter. When distended, pressures of 75 PSI or 5 Atm are generated for effective dilatation.

Minor complications have occurred in the biliary tree (fever, 6; cholangitis, 1), and mild, uncomplicated pancreatitis has been experienced following manipulation of the pancreatic duct. This latter problem has been minimized, however, by insertion of a pancreatic drain following dilatation. This technique offers a new therapeutic approach to both benign and malignant strictures of the biliary tree and pancreas. The procedure is both safe and tolerated as well as other diagnostic endoscopic procedures, and it may be easily repeated, thus avoiding more uncomfortable invasive approaches. Long-term follow-up of cases in which this procedure was employed are awaited.

Transpapillary Endoscopic Endoprostheses

For the past four years, nonsurgical decompression techniques for preoperative and/or palliative treatment of obstructive jaundice have been available (37–45). Both percutaneous and endoscopic techniques are effectively used in the management of this clinical problem. Recently, production model endoscopes with large channel diameters have become available to accommodate larger drains, thus eliminating the restrictions due to channel size of the endoscopes. I have been using a new endoscope (JFIT 3.7 Olympus Corporation of America) with a much larger channel

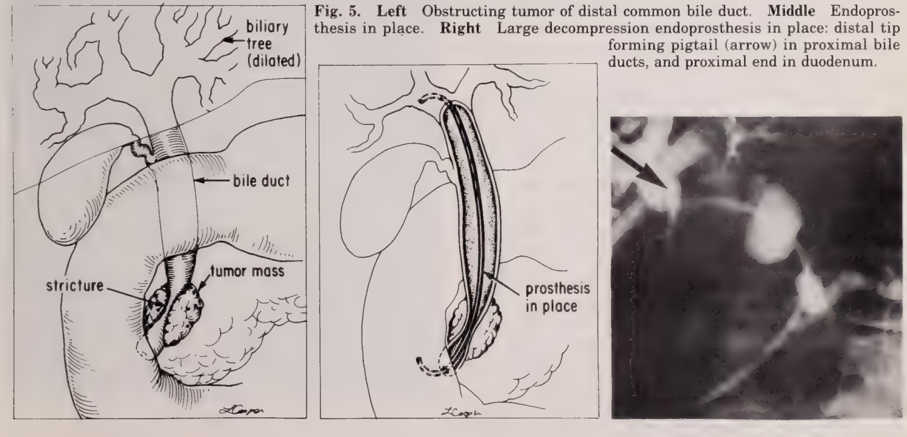

Fig. 5. **Left** Obstructing tumor of distal common bile duct. **Middle** Endoprosthesis in place. **Right** Large decompression endoprosthesis in place: distal tip forming pigtail (arrow) in proximal bile ducts, and proximal end in duodenum.

TABLE 5
Endoscopic Hydrostatic Dilatation
(N = 80)

	No.	Improved No. (%)
Biliary tree		48 (60)
Bile duct strictures	14	
Hepatic 9		
Bile 5		
Papillary stenosis/dyskinesia	54	
Pancreatic duct strictures	18	8

that permits insertion of drains as large as 10F (46, 47). These larger drains offer the advantage of increased flow rates, thus reducing frequency of cholangitis and recurrent obstruction attendant with smaller drains. Prior use of Teflon dilating catheters, 5F to 10F (Cook, Inc., Bloomington, Indiana), facilitates the insertion of large drains (Fig. 5).

Selective insertion of two catheters into right and left hepatic ducts for strictures of the common hepatic duct have been successful on five occasions (Fig. 6). Using the endoprosthesis or opacified duct as a guide, percutaneous thin needle aspiration biopsies are performed for histologic diagnosis. The positive yield of this technique is encouraging, and morbidity is low (48, 49).

Endoscopic insertion of a transpapillary endoprosthesis provides internal drainage of bile, restoring flow; clotting factors; and electrolyte and fluid balance. The complications associated with these drains are infrequent and less serious; they consist mainly of partial or complete obstruction, or cholangitis, or both. Servicing these drains by endoscopic irrigation or exchange is easily accomplished, and intended function is restored with minimal intervention. On the other hand, percutaneous drains contain external appliances that may expose the apparatus to microorganisms and infection. Also, the insertion of percutaneous catheters through the thoracic cavity, peritoneum, and liver may result in bleeding and dislodgement, peritonitis, and pneumothorax. An endoprosthesis may be placed percutaneously, but if it becomes occluded, further interventional techniques or either irrigation or exchange are required.

To date, 208 endoprostheses in my series (one hundred thirty-two 9F and 10F) have been successfully inserted in 233 attempts (89%). Two patients have been followed up for as long as 20 months. However, the mean survival for carcinoma of the pancreas after decompression has been only two months. Most patients were desperately ill at the time of insertion of the prosthesis. One hundred sixteen patients were discharged home, 67 subsequently underwent surgery, and the remainder died in hospital.

Bilirubin levels are effectively decreased by endoscopic decompression to a mean of 2 to 3 mg/dl per day, a result also obtained with percutaneous drains. Alkaline phosphatase levels are slower to respond, but a 50% to 70% reduction in three to five weeks is expected. No clinical evidence of pancreatitis has occurred after catheter placement in the papilla, even with apparent catheter occlusion of the orifice. Improved clinical status and life style occur with this conservative approach, and no external apparatus is required.

The comparable success rates of ERCP and PTC for decompression are due to advances in endoscopy as well as in the current state of the art. My preference at this time for palliative treatment of malignant obstruction is the endoscopic endoprosthesis, because drainage occurs more naturally and external hardware is not required. However, either method of drainage appears to im-

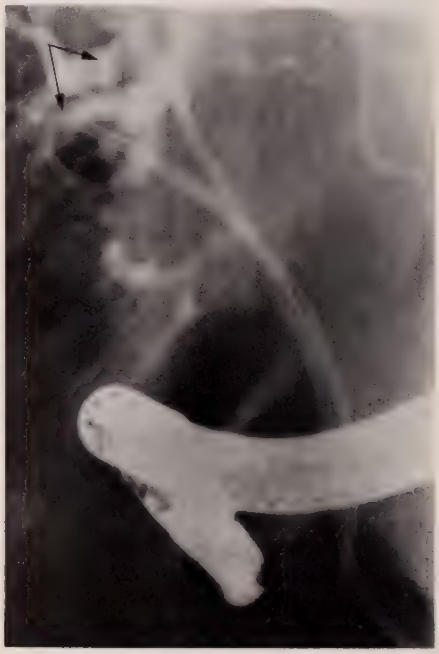

Fig. 6. Radiograph obtained in patient with obstructing lesion in common hepatic duct. Pigtail endoprostheses in right and left hepatic ducts (arrows).

prove survival and the quality of life for the patient, if used palliatively, and current studies indicate that improved surgical morbidity and mortality rates are attendant with preoperative decompression (51, 52).

Summary

Endoscopic retrograde cholangiopancreatography has been rapidly accepted as a new diagnostic and therapeutic approach to the management of obstructive jaundice and has become a part of our armamentarium. When this procedure is combined with percutaneous techniques, the total management of many manifestations of liver and pancreatic disease is possible, especially in patients with unresectable neoplasms. The choice of technique is usually dependent upon expertise, but serious consideration should be given to patient comfort and cost effectiveness—factors that strongly favor the endoscopic approach.

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Splenic Cystectomy and Splenic Preservation

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Richard Marshak did not believe the practice of medicine was immutable, carved in stone. He diligently searched to define frontiers and then extended them. He set us a fine example, and we must follow.

The recent change in attitude toward splenectomy is but one example. The pendulum in the management of splenic cysts has swung from partial splenectomy, which was considered to be of "historic interest only" when the cyst would be unroofed and drained for several weeks (1), to the modern approach, which has been total splenectomy. Recently, however, Morgenstern strongly advocated a return to partial splenectomy (2), recognizing the incidence of sudden, overwhelming infection associated with complete removal of this organ.

This recognition was initiated by King and Schumacker's report (3) of overwhelming sepsis in five infants who had undergone splenectomy for hereditary spherocytosis in 1952, and supported by further reports of long-term effects of splenectomy and infection (4, 5).

The first attempts at splenic repair were only intermittently successful (6–8), but a major impetus was Mishalany's repair of the spleen in an 8-year-old boy in 1974 (9). Morgenstern's work, especially, has had a significant impact on acceptance of splenic preservation (10, 11), but the techniques for splenorrhaphy have never been satisfactory. These have included the use of topical hemostatic agents, capsular sutures, mass mattress sutures, and arterial ligation. Such attempts at preserving spleens may result in an increased incidence of secondary splenic cysts, so defined because they have no cellular lining (1). These nonparasitic or secondary splenic cysts arise from spontaneous or traumatic subcapsular hemorrhage of the spleen and were rarely seen when standard surgical practice was to remove all injured spleens, even when they were not actively bleeding.

In 1982, successful use of the ultrasonic scalpel to provide rapid and efficacious splenic transection opened new horizons (12, 13). It was logical to use ultrasonic partial splenectomy in the management of a splenic cyst to preserve the remainder of the spleen.

Case Report. Patients with a splenic cyst frequently have atypical histories. My example, a 50-year-old man, had a 12-day history of epigastric and left upper quadrant pain. This pain was somewhat relieved by eating but worsened at night and increased in the three to four days prior to the patient's admission. During this time, he had no bowel motion and vomited on several occasions. He also complained of fever and sweats for 15 days' duration.

He had a similar episode six to eight months prior to admission; on that occasion, the pain lasted four to five days and was relieved by antacids. He lost 15 lb over this time and was somewhat anorexic. He routinely took aspirin once or twice a week and was an alcoholic with diabetes mellitus.

He was thin and mildly febrile (temperature 37.9°C). There was some left upper quadrant tenderness.

His white blood count was 12.8, and his chest x-ray showed a raised left hemidiaphragm with no associated effusion. An upper gastrointestinal series first revealed a large retrogastric mass affecting the fundus and the proximal portion of the body of the stomach, consistent with carcinoma of the stomach with metastases to adjacent lymph nodes. Upper gastrointestinal endoscopy demon-

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strated a necrotic ulcerative lesion in the body of the stomach. Biopsies of the ulcer showed only chronic inflammatory tissue. The liver/spleen scan showed a filling defect in the region of the spleen.

The definitive investigation in this case was the ultrasound scan, which showed a 10 × 12 × 14 cm cystic lesion in the spleen. Its position corresponded to the previously noted defects on investigation. At this point, the patient admitted a history of old left upper quadrant trauma.

Through an upper midline incision, the spleen was mobilized to the midline. It was then clear that there was a large traumatic pseudocyst of the spleen, and the area of fluctuation was identified and aspirated, yielding old, decomposed blood; 800cc of the chocolate-colored fluid was removed.

The alternatives for the management of this patient were splenectomy or unroofing the cyst and drainage. A further alternative was to remove the entire cyst, leaving a raw but nonbleeding splenic surface. A convenient technique to achieve this effect is to use the ultrasonic scalpel. First, however, it was necessary to cut through the fibrous wall of the cyst down to normal splenic tissue using the cold knife (Fig. 1) and the Bovie to control vessels. The ultrasonic scalpel then easily removed the large amount of tenacious old clot, associated with fibrous infiltrates, from the ulcerated surface of the spleen (Fig. 2). A clean, raw splenic surface remained; it appeared to be polished or bonded. Only occasional remaining bleeding points needed to be controlled with suture ligation with No. 000 silk.

As this had never been done before, it was decided that a large drain was safer than a small drain. In retrospect, a Hemovac would have been sufficient. Nonetheless, we used a large sump drain with a Penrose drain in the left upper quadrant. The patient had an uneventful postoperative course.

The Instrument. The Cavitron Ultrasonic Surgical Aspirator (CUSA system) is the ultrasonic scalpel. This instrument was first produced in 1976 and was used in the resection of neurogenic tumors (14). More recently, it has been used in general surgery, particularly in the dissection of solid organs (15–17). It consists of a control and power console with a separate gas sterilizable handpiece weighing only 8 oz. The pencil-grip surgical handpiece contains a magnetostrictive device, essentially a transducer vibrating longitudinally in response to an alternating electric current of 23 kHz. Through a connecting body, this causes a conical hollow titanium tip to vibrate simultaneously, with a maximal stroke of 300 μ. The handpiece is cooled by water, and a separate stream of cool saline irrigates the tip under a plastic flue.

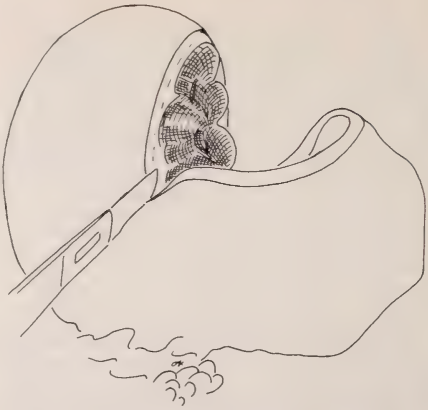

Fig. 1. Before using ultrasonic scalpel, it is necessary to cut through fibrous wall of cyst down to normal splenic tissue using cold knife and Bovie to control vessels.

Target tissue cells are imploded and fragmented when touched by the vibrating exposed tip. The fragmented tissue is then aspirated from the operative field. There is a differential effect on the parenchyma and on blood vessels. The parenchyma is very easily fragmented, but blood vessels, because of their high collagen content, are much more difficult to fragment. This tactile feedback allows the surgeon to spare blood vessels, to skeletonize them, and to remove suitable tissue millimeter by millimeter.

The initial work in the general surgical use of this instrument was done at the Veterans Administration Medical Center in the Bronx, NY, and at The Mount Sinai Medical Center in New York (15).

Discussion. Splenic cysts must first be diagnosed and, as indicated, patients with these lesions often have an atypical history. A space occupying lesion is often found in the left upper quadrant and is then identified by ultrasound scan as a cyst. Splenic cysts must then be differentiated from cysts arising from the pancreas, left lobe of the liver, mesentery, left kidney, and left ovary. If a history of trauma can be obtained, even at a late stage of investigation, a splenic cyst can be suspected. The presence of a large abdominal mass in the left upper quadrant also tends to

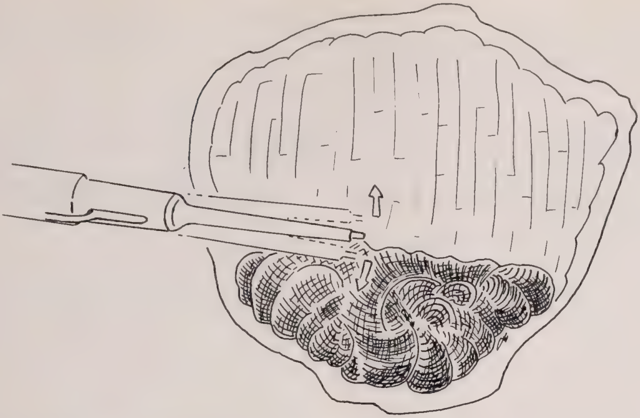

Fig. 2. Ultrasonic scalpel used to remove tenacious old clot from ulcerated surface of spleen.

prove the diagnosis. However, the absence of such a mass does not always exclude a splenic cyst. The cyst may be behind the costal margin.

The indications for surgery in these cases are (a) recurrent symptoms of pain and anorexia and (b) the signs of fever, infection, and weight loss.

Splenectomy results in an unexpected rate of death from sepsis of 0.65%, compared with 0.01% for the normal population (18). Although this overall incidence is low, it does represent a 60% increase over the normal in sepsis; moreover, approximately 50% of cases of sepsis end with death (19).

Thus, although a powerful argument can be made in favor of preserving the spleen, there is no point in performing a procedure if, as a result of it, septic drainage occurs for a minimum of some weeks. This has occurred because it has been impossible to remove the tenacious old blood clot from the parenchyma without uncontrollable bleeding.

This case illustrates that by using the ultrasonic scalpel, this problem could be overcome because the tenacious material was quickly removed from the splenic parenchyma, leaving a raw but "polished" surface. This is not quite as strange as it sounds; histologic specimens have shown a "bonded" effect after ultrasonic incisions—the surface is covered with a layer of very adherent red cells (20). The ease with which the tenacious old clot was removed, leaving a remarkably dry surface, attests to the advantages of this new technique. The patient's completely straightforward postoperative course without evidence of infection also attests to the advantages of this method.

Further, inadequate drainage of a splenic cyst will result in recurrence of the cyst. The tendency has been to avoid excising much of the wall of the cyst for fear of entering the splenic parenchyma, with subsequent uncontrollable bleeding. This clearly was avoided in the case reported by using the ultrasonic scalpel, which "sealed" the raw splenic surface. This method seems to be an improvement in the management of splenic cysts.

Summary. Partial rather than complete splenectomy for trauma is becoming accepted where feasible. Spleen preserving techniques were difficult to apply before the advent of the ultrasonic scalpel. This paper presents a case of the successful use of this instrument in cleanly removing a splenic cyst while preserving the spleen. It also advocates the continued use of the ultrasonic scalpel.

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Percutaneous Drainage of Abdominal Abscesses and Fluid Collections

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Percutaneous drainage of abdominal abscesses and fluid collections has been described as "one of the great advances in modern surgery" (1) and is now a widely performed interventional radiologic procedure. This discussion reviews certain current technical concepts (2–9).

Fluid Aspiration

Guidance. Many fluid aspirations can be performed under real-time ultrasound guidance if they are large enough or superficial. The key concern is to be certain that no bowel loops intervene. If there is any question, CT should be performed. The worst sin is to traverse a loop of bowel and contaminate a sterile fluid collection, converting it into an abscess. However, because a diagnostic tap is so quickly performed and so definitive if fluid is retrieved, all needle procedures should be first considered for ultrasonography (US) guidance, and only then triaged to computerized tomography (CT).

Localizing Techniques. Using real-time sonography, the tip of the needle is relatively easily visible in fluid collections, as opposed to solid lesions. Similarly, once a needle tip has entered the fluid collection, confirmation is immediately evident because fluid is easily aspirated. Jiggling the needle shaft will cause simultaneous movement of the tip with the transducer probe held off-angle or at right angles. Specialized snap-on needle holder adaptor assemblies advertised by commercial firms have not proven especially necessary or helpful.

Diagnostic Specificity of Ultrasonography and CT. The imaging appearance of fluid collections is often not sufficiently precise to determine whether the fluid is blood, pus, phlegmon, and so on. Therefore, in the vast majority of cases in which a fluid collection is seen in the presence of a fever, needle aspiration is required. Analysis of the sample should include at least a Gram stain for white cells and organisms. Pyogenic abscesses contain both. Sterile abscesses contain white cells but no organisms. Bowel contents contain organisms but no white cells.

Drainability of Cavity Contents. It is usually impossible to tell from the US/CT appearance whether a fluid collection is liquid enough to be drained by a catheter. A therapeutic trial of catheter insertion is often required. The thicker the fluid, the larger the catheter caliber required. Nevertheless, gelatinous nonliquid clot and phlegmonous pancreatic necrosis can rarely be drained successfully.

Abscess and Fluid Drainage

The following comments are based on my experience with over 300 cases (2–4).

Indications have broadened since the introduction of the technique several years ago. At present any fluid collection with a safe access route is a candidate for percutaneous catheter drainage. This includes collections in unusual locations, such as the presacral space, the lesser peritoneal sac and the ileopsoas muscle. In most instances a therapeutic trial of drainage will be necessary to determine whether the fluid collection is in fact liquid enough to be drainable. Many abscesses will be shown to have a causal underlying fistula, which is generally not discovered until several days after the abscess itself has been drained.

Acutely ill or moribund patients are also candidates for drainage as a temporizing maneuver even if the percutaneous approach is not considered likely to be curative. Elective definitive sur-

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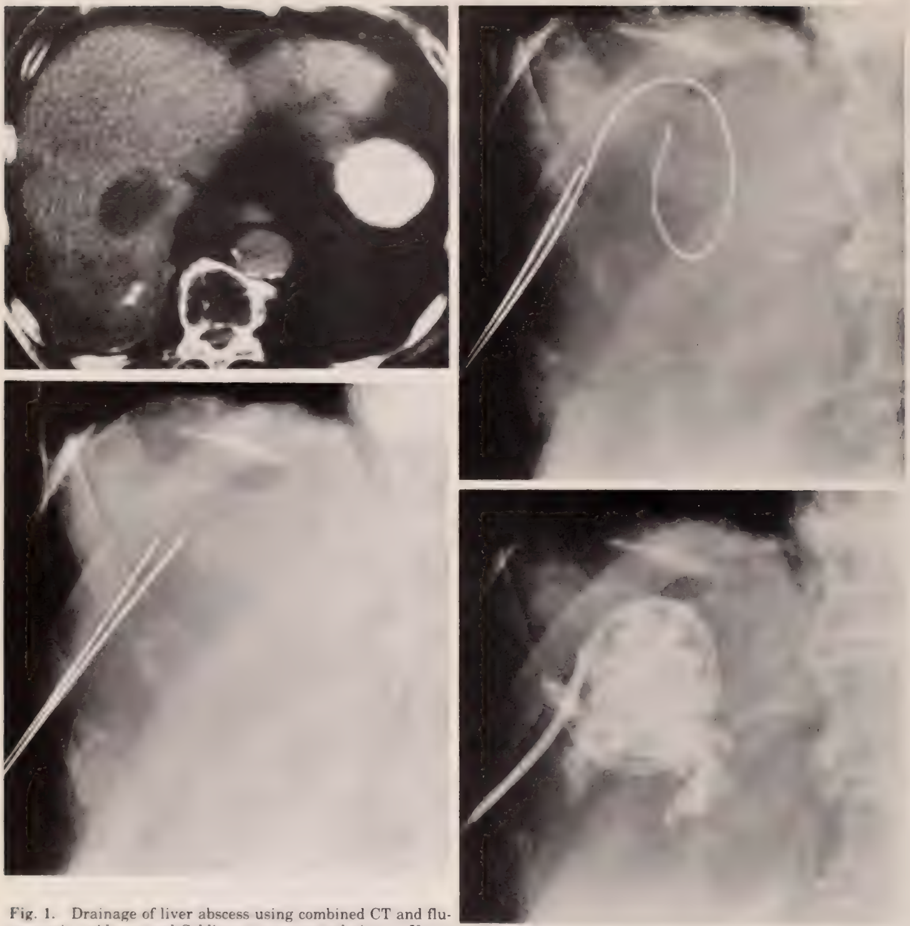

Fig. 1. Drainage of liver abscess using combined CT and fluoroscopic guidance and Seldinger two-step technique. **Upper left** Initial CT scan showing low attenuation lesion in posterior right hepatic lobe. Focus of parenchymal liver calcification is seen immediately behind lesion. **Upper right** Diagnostic needle aspiration performed under fluoroscopic guidance based on approximate localization provided by CT. A dual tandem 20 gauge needle and 18 gauge sheath technique were used. **Lower left** Following successful aspiration of pus, guide wire has been inserted and contrast medium injected, outlining extent of cavity. **Lower right** Abscess drainage catheter has been inserted and contrast medium injected, outlining extent of cavity.

gical drainage can then be carried out after resuscitative measures are administered.

Access Route Planning. Route planning is the critical issue from a technical standpoint. Originally, retroperitoneal and dependent access routes were the primary approaches employed. At present any access route including transperitoneal and nondependent is acceptable providing there is no intervening bowel or contamination of sterile spaces (pleura). In addition, transorgan approaches (transhepatic, transgastric) to lesser sac pancreatic collections have also been used successfully.

For image guidance, CT is particularly valuable for access route planning to establish regional topographic relationships and locate the presence of intervening contrast opacified loops of bowel. However, other imaging modalities are often useful, including ultrasonography and fluoroscopy, especially when angled needle approaches are made. Ultrasound and fluoroscopy add tremendous speed and flexibility to the procedure and it is increasingly common to combine CT guidance with real-time ultrasound or fluoroscopy.

The Catheter. Both Seldinger (2 step) and trocar (single step) insertion techniques are employed. The trocar techniques are most widely used for large or superficial collections (Figs. 1, 2).

Almost any catheter can be used to drain an abscess of fluid collection, although specially designed double-lumen sump catheters (vanSonnenberg) have been most widely popularized (Fig. 3) (5). These are soft-walled catheters, fitted with an inner metal introducer and stylet, and are available in 12–14 F size with large side holes. The vanSonnenberg catheter can be introduced using either a trocar or Seldinger technique.

Pigtails and tip retention devices are less important in abscess drainage than in biliary or in urinary drainage because the duration of catheter drainage is seldom more than 10–14 days and catheter dislodgement is less of a problem.

Radiology vs. Surgery. The early skepticism of experienced surgeons that small-caliber radiologic catheters could be effective in draining abscesses has given way to a general desire to understand the mechanisms of success (4). They are as follows:

1. Both surgical and radiologic drainage have their major beneficial effect almost immediately at the time of initial catheter placement. Evacuation of pus can result in recovery of a critically ill unstable patient in a matter of hours with either method. Use of sumps, drains, and tubes undoubtedly adds to the therapeutic effect over time, but the major benefit occurs immediately.
2. The thoroughness of cavity emptying by visual inspection (surgery) versus imaging may favor the radiologic approach because it is more precise, especially for complex or multiloculated collections. More accurate tailored placement of side holes is certainly an advantage of the radiologic approach.
3. Although surgeons have traditionally used large-bore catheter drains and sumps, since the major therapeutic effect occurs nearly instantaneously, the smaller bore radiologic catheters are quite adequate to drain residual fluid or convey irrigant solutions. This is especially true since irrigation at the time of initial catheter placement is routinely performed to remove the thickest material.

Pitfalls: Avoiding the Pleura. Localization of the posterior costophrenic sulcus on CT scans is often confusing, especially when there is a combined subphrenic and pleural fluid. Use of a fluoroscopic guided needle insertion in combination with initial ultrasound/CT imaging expedites catheter insertion. Transgression of the pleura is probably more frequent in biliary drainage work than with abscess or biopsy work, however.

Special Considerations

Pancreatic Abscess. Catheter drainage of pancreatic abscess can be curative but patient selec-

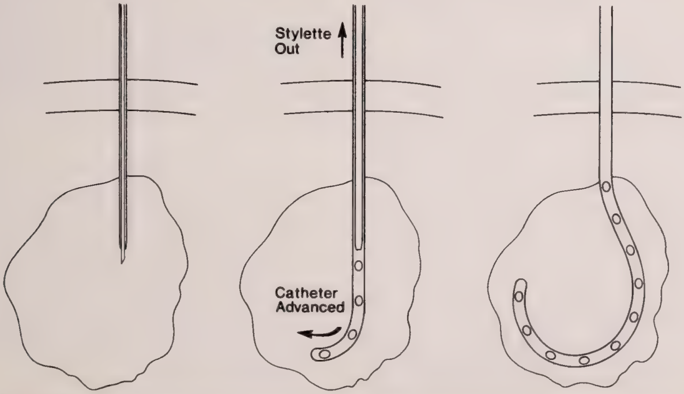

Fig. 2. Schematic drawing showing single-step trocar technique for draining abscess or fluid collection.

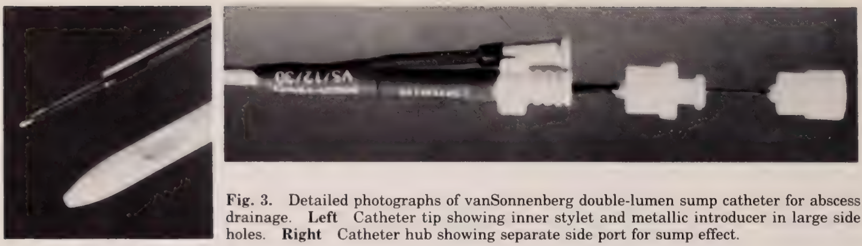

Fig. 3. Detailed photographs of vanSonnenberg double-lumen sump catheter for abscess drainage. **Left** Catheter tip showing inner stylet and metallic introducer in large side holes. **Right** Catheter hub showing separate side port for sump effect.

tion is important. Obviously, with diffuse phlegmonous pancreatic inflammatory disease especially with thick necrotic pancreatic tissue, complete cure with one or more percutaneous catheters cannot be guaranteed. Such patients are obviously moribund and although complete cure is not possible, a temporizing effect may be achieved with restoration of metabolic, fluid, and respiratory status, so that subsequent elective surgery can be carried out (10). Whenever possible a retroperitoneal route should be elected.

Pancreatic Pseudocysts. These pseudocysts are a continuing dilemma. The critical issue is to avoid contaminating the cyst, principally by scrupulous attention to access route planning. Recently, transorgan access via transhepatic and transgastric approaches have been used successfully. An issue of secondary importance is the presence of communication with the pancreatic duct and the presence of pancreatic duct obstruction as demonstrated by ductography. If there is open communication with the pseudocyst and the underlying duct anatomy is abnormal, catheter drainage is unlikely to succeed. Few institutions attempt percutaneous drainage of pseudocysts with great enthusiasm.

Abscess-Fistula Relationship. Many postoperative abscesses subjected to percutaneous catheter drainage will be found to arise from underlying fistulae from bowel, biliary, or urinary sources. Diagnosis is made by observing a sudden increase in flow via the abscess drainage catheter, usually on the seventh to tenth day after successful abscess drainage (6). Confirmation is obtained by contrast sinography of the catheter.

Complete nonoperative treatment can be accomplished by adjusting the abscess catheter to completely drain the leaking fluid by tailored side hole positioning. Use of a second or third catheter, diversion of the bile, bowel content, or urine flow by another catheter or tube may assist healing. Usually a more prolonged period of catheter drainage of a fistula (2–3 weeks) is required, but complete healing can be expected in most cases, provided there is no obstruction distally.

Mucomyst. This protein-cleaving agent (acetylcysteine) has been advocated as an aid to liquefying thick tenacious debris (8). However, there is no convincing experimental or clinical evidence to confirm its efficacy, and it should not be used as a substitute for more direct maneuvers, such as catheter adjustments in patients who are doing poorly after catheter drainage (9). Thus, readjustment of catheter position or CT scanning for multiple undrained collections should be instituted prior to instillation of mucomyst. In fact, it is likely that simple saline irrigations have as much effect in liquefying proteinaceous debris as this rather expensive chemical agent.

Summary. Percutaneous drainage effectively supplements antibiotics and surgery as an additional mode of therapy for intraabdominal abscesses. In perhaps the majority of cases it is now the treatment of choice, offering short-term, low morbidity, and widely applicable treatment with a high expectation of success. Surgery should be reserved for inaccessible collections or radiologic failures. The technical data in this review will I hope be of value to radiologists considering or performing this procedure.

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Entrainment of Microspheres within Blood Flowing through Microarteries

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Abstract

The forces and conditions that influence the distribution of non-water-soluble particles in vivo are not well understood. A knowledge of such forces may become important in designing delivery systems for the transport of non-water-soluble drugs and contrast agents. In vivo observations have shown that spherical blood-borne particles do not always distribute randomly. Sometimes formations are observed that suggest that interactions occur which lead to dependent relationships among particles (entrainment). Such interactions could potentially be useful in directing the flow behavior of blood-borne particles. To ascertain whether such particle-particle dependent relationships ever occur within blood in vivo, we cine photographed the time-dependent trajectories of 1,719 carbonized microspheres, 10-μm diameter, and 1,743 methylene-blue stained mulberry pollen grains 13-μm in diameter, as they flowed through microarteries of the hamster cheek pouch. For carbonized microspheres, 20 microarteries were studied; for pollen grains, 21 were studied. The temporal sequence and radial position of each microsphere was entered into an 8×8 contingency table and was tested for a dependent relationship among microspheres.

A positive entrainment phenomenon was present in 2/20 carbonized microsphere-containing vessels ($p < .0001, .01$); a negative entrainment phenomenon was found in 1/20 ($p < 0.01$).

No positive entrainment phenomenon was found with the pollen grain microspheres. In 1/21 microarteries containing pollen grain, a negative entrainment phenomenon was demonstrated ($p < .01$). In 4 other of these microarteries, a strong statistical trend toward negative entrainment was evident ($0.05 < p < 0.10$).

These findings suggest that spherical microparticles suspended in blood may sometimes perturb their environments sufficiently to affect the flow distribution of nearby particles.

The factors which influence the distribution of blood-born particles are not well understood. A fundamental understanding of such factors could potentially lead to the development of drug and contrast delivery systems in which alterations in the characteristics of a transport particle could alter its regional distribution. Several factors have already been identified which significantly alter the intravascular distribution of spherical microparticles (microspheres) in small tissue regions. Microsphere size is important and small differences, such as between a diameter of 9 μm and 15 μm, can significantly change the in vivo distribution of microspheres within organs (1, 2). The surface charge of a microsphere has recently also been identified as influencing its intravascular distribution in microarteries (3).

In vivo microscopy has shown that microspheres sometimes tend to group in some small tissue regions—several microspheres lodging in one microartery or its branches—whereas other regions do not contain any microspheres (4). One possible cause of this grouping is that conditions exist within the microvasculature which result in microspheres distributing within flowing blood in nonrandom formations. For example, microspheres may not distribute homogeneously across

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the microarterial lumen (5). Sometimes microspheres flowing within blood align in short columns, as though there were some particle-particle dependent phenomenon occurring. Such particle-dependent relationships in vivo have not been reported previously. Our purpose was to investigate an experimental in vivo approach for determining whether flowing particles can perturb their in vivo environment sufficiently to affect the flow distribution of other particles.

Materials and Methods

Background. In vivo observation of microspheres of 10–15 μm in diameter flowing through microarteries showed that they sometimes flowed in columns parallel to the microarterial lumen. The relationship between two or more consecutive microspheres can be either dependent or independent. We define as "entrainment" an occurrence in which consecutive microspheres flow one behind the other with a higher frequency (positive entrainment) or lower frequency (negative entrainment) than expected on the basis of the two-dimensional radial distribution of all microspheres flowing through the lumen of the microartery. Entrainment implies a dependent relationship. The corresponding independent phenomenon of a greater than expected flux percentage of all microspheres flowing through one or more assigned two-dimensional spatial channels is defined as "channeling."

Animal Preparation. Twenty-eight male golden hamsters (*Mesocricetus auratus*) were anesthetized with intraperitoneal sodium pentobarbital (40 mg/kg). A tracheostomy tube was inserted and connected to a rodent respirator (Rodent Respirator Model 680, Harvard Apparatus Company, Dover, Mass.), cycling at 80 × /min with a stroke volume of 3 ml. The hamster's right carotid artery was cannulated and a polyethylene PE 10 (I.D. 0.28 mm, O.D. 0.61 mm) catheter (Clay Adams, New York, NY) was inserted through an arteriotomy and led towards the left ventricle. The hamster's left cheek pouch was prepared for vital microscopy using a single membrane preparation (6). The animal was then placed on the stage of an upright compound-light microscope, with the the plane of the cheek pouch horizontal and perpendicular to the viewing assembly and recording system (5). We examined the cheek pouch and selected for study a branch-free, relatively straight arterial segment, 25–55 μm in diameter and approximately 500 μm long. Standard electroencephalographic needle electrodes were used in obtaining electrocardiograms.

Microspheres. We used two separate batches of carbonized, nonradioactive microspheres (Minnesota Mining Mfg. Co., St. Paul, Minn), which had the manufacturer's specification of a diameter 8–10 μm and a specific gravity of 1.23 g/cm^3 (3M Co., Nuclear Products, St. Paul, Minn). Light microscopic examination showed that the first batch of microspheres were 9.9 ± SD 0.8 μm in diameter (N = 200), and the second batch measured 9.0 ± 0.6 μm in diameter (N = 180). The microspheres were ultrasonicated for 10 min, suspended to a concentration of approximately 10^6 microspheres/ml in 0.9% saline containing 1 unit of sodium heparin/ml, and then ultrasonicated again for 10 min.

The second type of microsphere was methylene-blue dyed paper mulberry pollen. Prior to each experiment, 100 mg of unhydrated paper mulberry pollen (Duke Scientific, Palo Alto, Cal) was placed in a centrifuge tube containing 1 ml of methylene blue solution (7). The methylene blue solution containing the suspended microspheres was then diluted 8:1 with 0.9% sodium chloride solution and centrifuged (Model HN, International Equipment Co., Needham Heights, Mass) at speeds just sufficient to sediment the pollen grains to the bottom of the tube within 5 min (300 xg). The supernatant was then pipetted from the microspheres and the pollen grains resuspended in 0.9% sodium chloride solution to a concentration of 10^6 particles/ml.

Light microscopic examination of the 200 methylene-blue stained microspheres showed that their shape approximated spheres whose diameter measured 13.2 ± 0.6 μm (3).

The microsphere suspension was drawn into a 1-ml syringe through a 27-gauge needle. The needle was inserted into the PE 10 catheter and 0.1 ml (approximately 10^5 microspheres) injected over 10 sec. Each hamster received only one type of microsphere. Continuous ECG recordings were made from 30 sec prior to injection until 30 seconds after injection.

Data Acquisition. We recorded the passage of microspheres through the hamster cheek-pouch arterial vasculature with a Redlake Locam 16 mm movie camera (Model 51-0002, Redlake, Co., Campbell, Cal), using Eastman Plus–X movie film 7231 (Eastman Kodak Co., Rochester, NY). The filming rate was 150 frames/sec. At the beginning of each cine film roll, a 50-μm-square counting chamber grid (American Optical Brightline Counting Chamber #1475, American Optical Co., Buffalo, NY) was placed on the microscope stage and filmed to establish magnification factors present in the optical/cine system.

The appreciable depth of focus of the light microscope we used was in excess of ±85 μm for resolving individual stationary microspheres (5). This distance was 1.4–4.4× larger than the diameter of the vessels observed.

Data Reduction. The data-reduction technique was similar to that previously described (5). In brief, the cine film was projected frame by frame onto a sheet of paper. The intimal walls of the projected vessel image were then drawn. A reference line was next drawn perpendicular to the vessel lumen. The reference line was subdivided into eight equal segments; the total length equaled the vessel diameter. As the projected image of a microsphere appeared on the tracing paper, its position was marked for each successive cine frame until it crossed the reference line. The temporal sequence and radial position of each microsphere crossing the reference line was tabulated.

Entrainment Test Statistics. The number of instances of a microsphere appearing in the i^{th} channel being followed by one in the j^{th} were tabulated for each vessel and reduced to an 8 × 8 contingency table of i rows and j columns: $i,j = 1,2,\ldots,8$. A microsphere in i row followed by a sphere in j column was listed as one observation in the ij^{th} cell, f_{ij} giving the frequency of observations for each cell. For a total of N microspheres there were $N - 1 = \Sigma f_{ij} = N^*$ observations. Row (r_i) and column (c_j) totals were then tabulated. The cell frequency which lay on the diagonal of the table, f_{ii}, represented the number of times a microsphere followed another in the same channel. If r_i was the total of i^{th} row of microspheres which were the first members of a sequential pair, then the probability of the second member of the pair appearing in the same channel was c_i, the column total for the same channel, divided by N^*. The expected cell frequency along the diagonal, $E(f_{ii})$, was compared with f_{ii} to test the greater or lesser than chance occurrence of the sequence (same channel pairs) observed along the diagonal.

$$E(f_{ii}) = \frac{r_i c_i}{N^*}$$

$$\text{Var } f_{ii} = r_i \left(\frac{c_i}{N^*}\right)\left(\frac{N^* - c_i}{N^*}\right)$$

The statistic

$$T = \frac{\sum_{1}^{8} f_{ii} - \sum_{1}^{8} E(f_{ii})}{\sqrt{\sum_{1}^{8} \text{Var } f_{ii}}}$$

tested the null hypothesis of no entrainment (8).

Results

The data base consisted of cine film observations on 1,734 pollen grain microspheres flowing through 21 microarteries in 14 hamsters and 1,719 carbonized microspheres flowing through 20 microarteries in 14 additional hamsters.

The statistic T of microsphere independence showed no positive entrainment for the vessels containing pollen grain. However, in 5 of 21 of these vessels, the p values were low, and the vessels had fewer than expected microspheres observed on the diagonal, that is, a negative T value: $T = 1.52$ ($p < .06$), $T = 1.32$ ($p < .09$), $T = 2.36$ ($p < .01$), $T = 1.34$ ($p < .09$), $T = 1.35$ ($p < .09$). The sign of the T statistics for the whole group was split: 11 negative and 10 positive. Group test data for carbonized microspheres showed two vessels (2/20) which strongly indicated positive entrainment: $T = 9.74$ ($p < .0001$), $T = 2.61$ ($p < .01$), and one vessel with negative entrainment ($p < 0.01$).

Discussion

In vivo microscopy has shown that carbonized microspheres sometimes tend to group in small tissue regions; that is, several microspheres lodge within one vessel or tissue region, whereas nearby vessels do not contain microspheres (4). Such observations raise the possibility that microspheres do not always distribute independently of one another and that forces or conditions may exist which cause microsphere interactions. Such a situation could come about if a microsphere perturbed its in vivo environment in such a manner as to influence the flow distribution of other microspheres. Such a phenomenon, which has not previously been documented in vivo, may be important in the distribution of the naturally occurring blood particles, such as erythrocytes and platelets; and understanding such effects could lead to the development of selective drug transport systems. Investigations aimed at analyzing the factors which are significant in blood-born particle distribution can be performed either in vivo or in vitro. The major advantages of in vitro systems lie in the ability to isolate and control experimental variables. However, because of the enormous complexity of biological systems, conclusions reached from in vitro experiments, which control only a limited number of variables, may not be highly applicable to in vivo situations.

In searching for the existence of a particle-particle dependent relationship, or entrainment, in vivo, we examined cine film of the passage of carbonized and pollen-grain microspheres as they flowed through microarteries of the hamster cheek pouch. We found that the microspheres sometimes flowed in short columns. To quantitate the in vivo relationship among microspheres, a statistical test was devised which measured the dependence of consecutive microspheres on one another (8). With this test, an entrainment phenomenon was statistically distinguishable from channeling, which had a similar cine film appearance. Channeling consists in a greater than expected percentage of all microspheres flowing through one or more assigned spatial channels. However, unlike entrainment, in channeling the relationship among microspheres is statistically independent. An example may help to distinguish entrainment from channeling. Suppose a photographer is standing on an overpass above a multilane, one-way highway and cine filming the flow of traffic. The film shows a number of cars driving down one lane, while the other highway lanes contain little traffic. An entrainment phenomenon is present if the relationship among the cars following one behind the other is dependent, as in a funeral procession or a convoy. A channeling phenomenon is present if the relationship among the cars is independent—the cars are driving in the same lane because of potholes or ice in the unused lane, or because the exit is on the frequented lane's side.

We emphasize the selectivity of the statistical test used for entrainment. The a priori probabilities by which expectation values for sequential pairs were calculated were taken from the observed microsphere-density distributions for the respective vessels. They implicitly included any channeling effects that occurred. The statistical test for entrainment was, therefore, not prejudiced either way by the presence of channeling. The effect of projection of the three-dimensional in vivo microsphere distributions onto the two-dimensional film plane was also reflected in the expectation values for sequential pairs. Thus, although one finds entries along the diagonal for sequential microspheres that were in the same horizontal distance interval but at different vertical depths, the off-diagonal entries are similarly overestimated. One would not expect the resulting statistical test to lead to a significant pair correlation where none exists for the full three-dimensional microsphere distribution.

Our results showed a positive entrainment phenomenon in 2 of 20 vessels containing carbonized microspheres ($p < .01$); a negative entrainment phenomenon was found in 1 of 20 of these vessels ($p < 0.01$). No positive entrainment phenomenon (0/21) was demonstrated in the vessels containing pollen grains. In 1 of 21 vessels, a negative entrainment phenomenon was demonstrated ($p < 0.01$) and in four others, a strong trend was evident ($0.10 < p < 0.05$). Therefore, our findings indicate that in vivo particles flowing in blood may, on occasion, perturb their environment sufficiently so that the flow distribution of nearby particles becomes affected.

The causes of the positive and negative entrainment phenomena demonstrated in these experiments is not known. The forces which act on suspended particles within blood include hydrodynamic (Newtonian) forces (noninertial and inertial); rheologic (non-Newtonian) forces; physical-chemical surface interactions (hydrogen bonding and van der Waals and coulombic forces; geometric factors (vessel cross-sectional shape, vessel curvature, and nature of linkage of branch points); and physiologic factors.

Certain of these forces probably do not contribute to either the entrainment or channeling that we observed. Spherically symmetric rigid particles do not experience any lateral forces for flows in the noninertial regime, i.e., beneath a particle Reynolds' number (Re_p) of 10^{-3} (9). In this study Re_p were generally $\sim 10^{-4}$, thus making it unlikely that inertial effects were involved in channeling or entrainment (Harell et al. Rheological vs inertial "pinches." Microvas Res 1980; 20:111–112).

Rheological forces theoretically could have a significant role in causing either positive or negative entrainment or channeling. Alignment effects have been observed experimentally among microspheres suspended in mildly elasticoviscous fluids at low rates of shear (10). Axially directed shear in such fluids causes randomly distributed microspheres to align in chains along streamlines. Such alignment phenomena are probably due to a normal stress interaction (11). Blood may have significant shear-dependent normal stresses (12). Such normal stresses in blood apparently present as a lateral force on the microsphere and probably affect particle migration across streamlines. This would be seen as channeling. The influence of normal stress deviates probably depends on several parameters, including the ratio of the particle diameter to the vessel-lumen diameter, the particle velocity, and the microsphere-microsphere distance. One theoretical study has indicated that a critical interparticle distance exists below which two particles are drawn together and line up along streamlines (13). Beyond this critical distance, however, the particles are repulsed from each other and forced

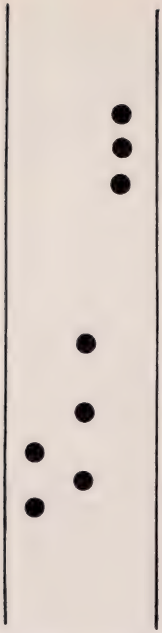

Fig. 1. Schematic representation of positive entrainment phenomenon. Microspheres flow in columns. Occurrence of consecutive microspheres, flowing one behind the other, is significantly higher than expected frequency determined on the basis of the two-dimensional distribution of all microspheres flowing within the microartery.

across streamlines. Theoretically, then, the normal stress deviate may contribute both to channeling and to a positive or negative entrainment phenomenon.

Physicochemical surface interactions between microspheres are unlikely to contribute either to channeling or entrainment. The longest range of the surface interactions listed above is coulombic, due to the diffuse ionic layer surrounding the macroscopic particle. Methylene-blue stained pollen grain microspheres carry a relatively strong negative surface charge compared to the 9-μm-diameter carbonized microsphere, which carries a much smaller negative surface charge (3). The upper limit for the falloff distance for coulombic interactions that one would expect for the strongly charged pollen-grain microspheres is on the order of 200 A (14). The cine films showed, however, that the mean intermicrosphere distances recorded were generally on the order of hundreds of microns. Thus, in the absence of actual collisions between microspheres, physicochemical microsphere-microsphere surface interactions probably did not significantly influence our findings. Microsphere collisons with the microarterial wall were much more frequently noted on cine film than microsphere-microsphere collisions. Microsphere-wall collisions could result in physicochemical interactions and possibly lead to either an increase or decrease in peripheral concentration which would be seen as channeling.

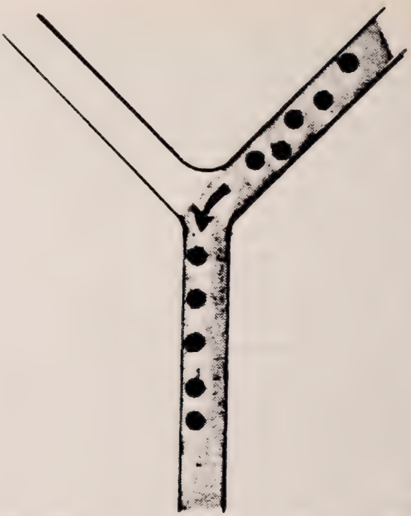

Fig. 2. Schematic example of channeling. Microspheres flow in curved or branched microartery. Centrifugal force displaces microspheres to vessel periphery. A preponderance of microspheres flow along one vessel wall, producing a nonhomogeneous distribution with a greater than expected percentage of all microspheres flowing through one spatial channel. The relationship among microspheres is statistically independent, since the occurrence of microspheres one behind the other is not statistically greater than predicted from recorded spatial distribution.

Geometric effects may also possibly play a significant role in causing channeling. If a microartery has sufficient curvature, centrifugal forces, owing to the greater density of microspheres than blood, will direct microspheres peripherally. Similarly, if the vessel's cross section deviates from cylindrical symmetry—for example, if one side of the vessel is narrower—the result would be a preponderance of microspheres flowing through the wider section of the vessel. This would produce channeling.

Physiological effects may result in the appearance of channeling or entrainment (Fig. 1). The

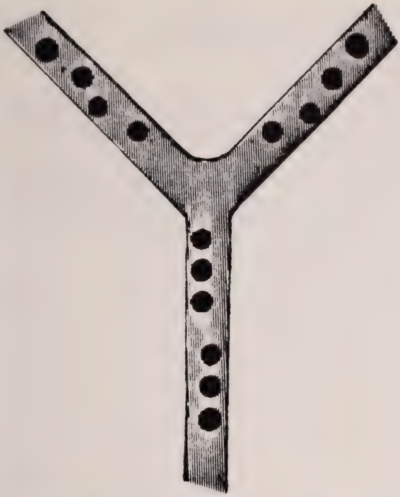

Fig. 3. A schematic example of alternating flow from either side of arterial-arterial arcade, which can result in either channeling or spurious entrainment, or both.

hamster cheek pouch contains numerous arterial-arterial arcades (15). Thus, some microarteries have two distinct arterial flow sources. If microspheres enter such a dual-source microartery from only one of its two flow sources, the microspheres will frequently flow to a region adjacent to only one of the two arterial walls. The result is channeling (Fig. 2). Should microspheres enter from both flow sources, the result may resemble either channeling or entrainment (Fig. 3). In vivo microscopy of the hamster cheek pouch has shown that occasionally microspheres will enter a microartery first from one side of an arcade, then from the other. This may lead to a transluminal microsphere distribution which first predominates along one side of the microarterial lumen and then the other. In such a situation, the frequency observed for one particle following another would be higher than calculated on the basis of random incidence for the two sides, and a statistically false positive entrainment effect may occur. Slightly more complex flow situations can also lead to spurious negative entrainment effects.

The experimental design employed in these experiments did not allow us to determine whether spurious entrainment occurred. The filmed axial length of microartery was a sufficient distance from any major branch points that these were not included within the recorded image. However, observations on other occasions of microsphere flow patterns within the hamster cheek pouch indicate that alternating microsphere flow from dual source microarteries is rare during the time intervals used in data gathering. In addition, most of the data in these experiments was not collected from dual source microarteries. Thus, spurious positive and negative entrainment due to alternating flow sources probably does not account for the entire entrainment effect observed in these experiments.

In vivo microscopy has documented that microspheres 10–15 μm in diameter do perturb their environment (4). When a microsphere impacts in a microartery, alterations in both the vascular activity and flow within the microartery may occur. Adjacent collateral flow may also develop (4). The present data indicates that microspheres may not only perturb their environment by impacting within a vessel, but may also, on occasion, alter the local flow environment in such a way as to cause microsphere interactions. Such interactions may be either positive or negative. The cause or causes of the entrainment phenomenon is not yet known, but an understanding of the forces involved may possibly lead to the development of selective drug delivery systems and help in understanding the in vivo distribution of naturally occurring blood particles.

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Twenty-First Bernard H. Eliasberg Memorial Symposium Recent Advances in Monitoring during Anesthesia

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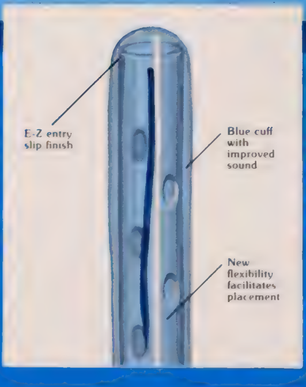
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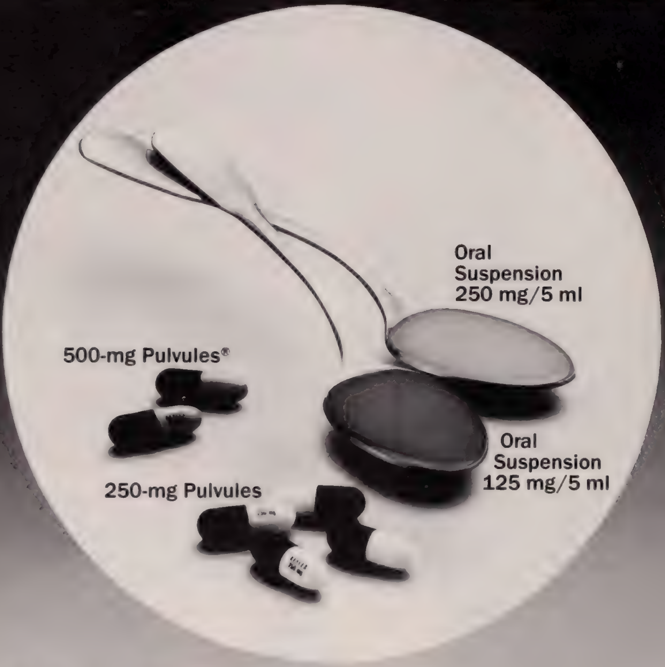
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CONTENTS

TWENTY-FIRST ELIASBERG MEMORIAL SYMPOSIUM
RECENT ADVANCES IN MONITORING DURING ANESTHESIA

Introduction *George Silvay, M.D., Ph.D.* 559

The History and Development of Cardiovascular Monitoring during Anesthesia *George Silvay, M.D., Ph.D., and Richard Griffin, B.M., FFARCS* 560

Operating Room Pollution *James B. Eisenkraft, M.D.* 564

Continuous Monitoring of Mixed Venous Oxygen Saturation in Clinical Practice *John C. McMichan, M.D., B.S., Ph.D.* 569

Intraoperative Esophageal Electrocardiography *Robert A. Kates, M.D.* 573

Pulmonary Artery Catheterization: Past, Present, and Future *Daniel M. Thys, M.D.* 578

Evoked Potentials in the Operating Room *Betty L. Grundy, M.D.* 585

Transesophageal Echocardiography *Joel A. Kaplan, M.D.* 592

Anesthesiology at the Turn of the Century: Where Do We Go from Here? *Nicholas M. Greene, M.D.* 595

Journal Awards 1984 601

The Low-T_3, Low-T_4 Syndrome of Nonthyroidal Illness: Adaptive Temporary Hypothyroidism *Barnett Zumoff, M.D.* 604

CASE REPORTS

Anesthetic Management of a Patient with Osler-Weber-Rendu Disease and Chronic Renal Failure *Harvey Plosker, M.D., and Raymond Miller, M.D.* 610

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CONTENTS *continued*

Infective Endocarditis in Hypertrophic Cardiomyopathy: Case Report and Review of Literature 1961–1982 *Reuven Zimlichman, M.D., and Ilya A. Ovsyshchler, M.D., Ph.D.* 614

SPECIALTY NOTES

GASTROENTEROLOGY *David B. Sachar, M.D., editor*

Clinical Applications of Gastrointestinal Motility Tests *Lawrence B. Cohen, M.D.* 620

NEUROLOGY *Allan E. Rubenstein, M.D., editor*

An Unusual Cause of Tetany: Surreptitious Use of Furosemide *Horacio Kaufmann, M.D., Fernando Elijovich, M.D., and Melvin D. Yahr, M.D.* 625

OPHTHALMOLOGY *Keith M. Zinn, M.D., editor*

Partial Avulsion of the Optic Nerve Head Secondary to Local Trauma: Case Report *Keith M. Zinn, M.D., and Elaine H. Kirban, M.D.* 629

RADIOLOGY *Jack G. Rabinowitz, M.D., editor*

Case 1 *Richard B. Ruchman, M.D., Rhona J. Keller, M.D., A. Sicular, M.D., and A. D. Hauser* 633

Case 2 *E. S. Gendal, M.D., Rhona J. Keller, M.D., A. Sicular, M.D., Jerome D. Waye, M.D., and A. Cornell, M.D.* 637

STUDENT'S CORNER *Howard Levin, M.S., editor*

Evoked Potentials in the Diagnosis, Prognosis, and Management of Neurologic and Neurosurgical Patients *Nathan Moskowitz, Ph.D.* 640

Arterioportal Fistula as Cause of Hypertension *Donald Pang, M.D.* 644

Corrections 646

LETTERS TO THE EDITOR

The Graffiti Pharmacopeia *Stephen J. Marks, M.D.* 647

Index to Advertisers

Allied/Regency Medical Laboratories	cover 3
Blue Cross and Blue Shield of Greater New York	cover 4
Bristol-Myers Co.	648
Eli Lilly and Company	ii
IHM Institute for Health Maintenance	i
Mon-a-therm, Inc.	cover 2

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The History and Development of Cardiovascular Monitoring during Anesthesia

George Silvay, M.D., Ph.D., and Richard Griffin, B.M., FFARCS

Soon after the introduction of clinical general anesthesia by W. T. G. Morton in 1846 and John Snow in 1847, the need to monitor patients was recognized. The first death under chloroform anesthesia, that of 15-year-old Hannah Greener in 1848, highlighted the importance of monitoring simple vital signs, such as the pulse, for changes in volume and rhythm and respiration. This paper traces briefly the history of cardiovascular monitoring during anesthesia. The observation that blood flows under pressure was made first on animals. The earliest source for correct observations of arterial and venous flow and pressures is William Harvey's *De motu cordis* (1), published in 1628. A century passed before Stephen Hales offered the first quantification of arterial blood pressure measured in the horse (2). The first cardiac catheterization was performed by Claude Bernard in 1844 (3).

Indirect Measurement of Arterial Blood Pressure. In 1901, during a visit to Italy, Harvey Cushing met Scipione Riva-Rocci who, a few years earlier, had developed a practical sphygmomanometer for measuring blood pressure indirectly (4). Subsequently, Cushing recommended the routine use of this sphygmomanometer to determine blood pressure during anesthesia (5). Since the return-to-flow method was employed, only the systolic pressure could be determined, and this with very little accuracy, as the cuff used was a bicycle inner tube, which obviously gave excessively high values. However, at that time, normal values for systolic pressure were not known and, more importantly, the instrument provided information on trends of blood pressure change.

In 1905, Korotkoff described the sounds heard when flow occurs distal to the deflating cuff (6). This, together with the use of a wider cuff advocated by von Recklinghausen (7), allowed more accurate determination of blood pressure and is the basis of routine auscultatory blood pressure monitoring in the operating room to this day. Further advances in the indirect measurement of blood pressure largely involved the development of alternative means of "sensing" systolic and diastolic points.

In 1931, von Recklinghausen (8) described a semiautomated device for measuring blood pressure known as an oscillotonometer. A double-cuff system is used, with the proximal cuff occluding the artery and the distal cuff acting as the sensor to detect the onset of arterial pulsations. Corall and Strunin (9) demonstrated that inversion of a new cuff gave high systolic readings but had no effect with a worn cuff. They stressed that proper use, maintenance, and cleaning of the unit was essential to obtain accurate measurements. Nevertheless, the instrument is no more accurate than the auscultatory method, and recently the validity of the diastolic point has been questioned (10).

The introduction of ultrasound into clinical medicine in the 1940s allowed the application of the Doppler shift principle to detect blood flow (11) and movement of the arterial wall under the distal edge of the sphygmomanometer cuff (12). The commercially available Arteriosonde (Roche) uses piezo-electric crystals to generate ultrasound at 3 mHz. The ultrasound is reflected off the vibrating arterial wall, causing a change in wave

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From the Department of Anesthesiology, Mount Sinai School of Medicine of the City University of New York. Address reprint requests to George Silvay, M.D., Ph.D., Department of Anesthesiology, The Mount Sinai Medical Center, One Gustave Levy Place, New York, NY 10029.

length (a Doppler shift), which is detected by receiving crystals and transmitted as an electronically conditioned audible signal. The device is accurate and has found its greatest application for measurement of blood pressure in infants (13).

Rapid transient changes in blood pressure can occur during anesthesia, especially during induction, emergence, certain surgical manipulations, and induced hypotension. Such changes can be easily missed if intermittent manual estimation of indirect blood pressure is used. Ideally, continuous direct intra-arterial pressure monitoring would be employed. However, the development of automated devices has allowed frequent estimation of indirect blood pressure. The Dinamap (Critikon) is essentially an oscillotonometer in which the cuff can be automatically inflated every 1 to 16 minutes. The instrument is simple to use and has been shown to produce accurate results (14). The Arteriosonde is also available in an automated form. Both these devices can produce a hard-copy record of blood pressure readings.

The Direct Measurement of Arterial Blood Pressure. Poiseuille (15), in 1828, described the mercury manometer. In 1847, Karl Ludwig made use of Poiseuille's device and applied it to his invention of the kymograph (16). A column of mercury on the kymograph moved, and thus directed a floating needle against a moving drum. This device allowed animal hemodynamic physiology to be recorded and continuously studied. The application to humans, however, was limited by problems of access and control of bleeding and infection. Almost one century later, direct recording of arterial blood pressure continued to be difficult, even though problems of sepsis and coagulation were solved.

The discovery of plastic "nonthrombogenic" sterile tubing and its medical applications occurred in 1945–46. In 1949, Lyle Peterson and Robert Dripps (17) described the technique of percutaneous placement of a plastic catheter for continuous measurement of arterial blood pressure during anesthesia and surgery. The value of this measurement was widely recognized, but the technique remained unpopular. The recording equipment was impractical and too expensive.

The technique of surgical cutdown was used to gain access to the artery during cardiac surgery in the 1950s. In 1960, the catheter over the needle was introduced, and the wide medical application of Teflon made possible convenient percutaneous access, leading to easier and smoother percutaneous placement of cannulae for continuous monitoring of arterial blood pressure. The ease of the technique allowed routine monitoring of direct arterial pressure by surgeons, anesthesiologists, and other physicians. The simultaneous technological advances in recording equipment have made invasive arterial monitoring commonplace in the operating room, intensive care unit, and recovery room.

The Electrocardiogram in the Operating Room. In 1918, Heard and Strauss (18) reported two cases of atrioventricular rhythm, one of which occurred immediately following ether anesthesia. They report that "no other cases of nodal rhythm have been oberved by us in a series of 21 cases in which electrocardiographic records have been taken during anesthesia." No further details were given.

Levine (19) reported two cases of paroxysmal atrial tachycardia under ether anesthesia, documented by electrocardiography. However, no prospective study of the practical use of the electrocardiograph (ECG) for monitoring patients in the operating room was reported until 1922. At that time, Lennox, Graves, and Levine (20) studied 50 operations performed on 49 patients at the Peter Bent Brigham Hospital in Boston. The monitoring method was admittedly less than ideal. The electrocardiographer was summoned by a buzzer in the operating room at the beginning and end of the operation and during critical moments in the operation! ECG tracings were produced by a string galvanometer, at average intervals of 2½ minutes. To get a permanent record, photographic paper had to be exposed to light. The heart rate calculated from the ECG tracings was much higher than the count of the anesthetist. The most marked discrepancies usually occurred during induction of anesthesia, when the pulse rate was taken by a nurse from the ward. Abnormalities of conduction (displacement of pacemaker) were found in 15 (30%) of the cases and 11 cases developed premature beats, 7 of them ventricular in origin. None of these premature beats were noted by the anesthetist. Analysis of the patients' characteristics, type of surgery, and type of anesthesia failed to demonstrate predisposing factors apart from alterations in vagal tone.

The value of the electrocardiogram during surgery was demonstrated by further similar studies (21–23). However, the intermittent nature of the recording and the inevitable delay in developing ECG tracings on photographic paper limited the usefulness of these observations for diagnosis and therapy. Direct-writing ECG recorders (24) eliminated the delay associated with processing films but were impractical for obtaining continuous records.

In 1952, Himmelstein and Scheiner (25) described a cardiotachoscope which permitted continuous display of the ECG on a cathode ray screen. The heart rate, obtained by measuring the time interval between successive beats, appeared as a moving line on the calibrated screen of a cathode ray tube. A direct writing cardiograph could be attached to the instrument to obtain permanent records.

With the advent of continuous monitoring, the routine use of the ECG to detect abnormalities of rhythm and rate became practical. Several reviews and studies (26, 27) documented the type and incidence of dysrhythmias which could occur during anesthesia. Lead II was usually monitored because the axis paralled the P wave vector producing a prominent P wave for easy recognition of dysrhythmias. The application of the ECG to detect myocardial ischemia during anesthesia was first proposed by Kaplan and King (28). In patients undergoing stress tests, Blackburn (29) had previously found that the majority of ischemic episodes can be detected by precordial lead V_5 of a 12-lead electrocardiogram. Kaplan (30) has demonstrated that this lead can be successfully used in the anesthetized patient, or a modified CM_5 lead can be used with the 3-wire system commonly found in the operating room.

More recently, technology developed outside the operating room has been applied to anesthetized patients. Twenty-four-hour Holter monitoring has been used to detect the frequency of dysrhythmias and ischemia (31) occurring in the perioperative period. Studies based on this technique have shown that the period of induction and the period immediately after recovery are particularly hazardous to the patient. However, this type of monitoring is essentially retrospective, and does not allow therapeutic intervention. Roy et al (32), using an exercise electrocardiographic monitor, found that 11 of 29 patients could be seen to develop ischemia when lead V_5 was monitored. Nine of the 11 ischemic episodes were not recognized on the standard operating room monitor (lead II). Closer monitoring of the ST segment seems clearly valuable. In the meantime, the routine use of the electrocardiograph in all patients to detect irregularities of rhythm and ischemia during anesthesia is now unquestionably accepted.

Cardiac Catheterization. Werner Forssmann is credited with being the first person to pass a catheter into the heart of a living person (33), using himself as the subject. At the age of 25, while receiving clinical instruction in surgery in Germany, he passed a urethral catheter through one of his left antecubital veins, guiding it by fluoroscopy (he looked through a mirror held by a nurse in front of the fluoroscope screen) until the catheter entered his right atrium. He then walked down the stairs to another floor, where the catheter position was documented by chest roentgenogram.

In 1930, Klein reported 11 catheterizations of the right side of the heart, including catheterization of the right ventricle and measurement of cardiac output in humans, using Fick's principle (34). In the 1940s, catheterization of the right side of the heart began to be used to investigate problems of cardiovascular physiology by Cournand (35), who later received the Nobel prize (together with Forssmann) for their pioneering efforts. In 1947 Dexter (36) and Werko (37) reported on oxygen saturation in the pulmonary artery and demonstrated, for the first time, the value of the pulmonary artery "wedge" pressure in evaluating events in the left side of the heart.

Further developments came rapidly: retrograde catheterization of the left side of the heart, transeptal catheterization, and in 1959, Sones' development of selective coronary angiography at the Cleveland Clinic (38).

In 1970, a balloon-tipped flow-guided catheter technique was introduced by Swan and Ganz, making possible the use of the catheter outside the catheterization laboratory, both at the bedside and in the operating room (39). Swan and Ganz developed a new catheter that could be carried passively by the blood stream through the right side of the heart to the pulmonary artery. The basis of the new concept was the combination of a flexible catheter and an inflated balloon at the tip.

This survey of the development of cardiovascular monitoring has outlined the beginning of techniques that nowadays we take for granted. However, as Shakespeare put it, "the past is prologue." More sophisticated techniques are now becoming practical for monitoring cardiovascular and other physiological systems during anesthesia. Some among these newer techniques are discussed in this issue—continuous mixed venous oxygen saturation, transesophageal electrocardiography, echocardiography. Further and as yet unforeseen developments in monitoring will continue to improve the care of patients under general and regional anesthesia. Nevertheless, the practice of feeling the pulse and monitoring breath sounds in order to maintain direct contact with the patient are still of cardinal importance for the clinical anesthesiologist.

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Operating Room Pollution

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Whenever inhaled anesthetics are used, the operating-room atmosphere may become contaminated by waste anesthetic gases. I discuss here three aspects of this topic: how we and the government became concerned about operating-room (OR) pollution; how to monitor the OR atmosphere; and whether anesthetics are really pollutants (the term "pollutant" implies a harmful substance, as opposed to "contaminant," which does not).

Great concern over trace concentrations of anesthetic gases began in 1967, when Vaisman (1) reported a survey of 354 anesthesiologists in Russia. All worked in poorly ventilated operating rooms and used nitrous oxide, halothane, and ether. Of the total, 303 responded; of these, 110 were women. Among female responders there were 31 pregnancies, 18 of which ended in spontaneous abortion. One pregnancy resulted in a congenitally abnormal child. The author concluded that these problems in pregnancy and other reported effects, such as nausea, irritability, and fatigue, were due to a combination of chronic inhalation of anesthetic vapors, emotional strain, and excessive work load.

Although uncontrolled and largely anecdotal, this study drew attention to the possibility that trace concentrations of anesthetics may be harmful. The matter was taken up by investigators in the United Kingdom (2, 3) and in Scandinavia (4), and their results appeared to confirm Vaisman's findings.

In 1970, Congress passed the Occupational Safety and Health Act (5), the purpose of which was to ensure "safe and healthful working conditions, for all men and women in the nation." The act established NIOSH, the National Institute for Occupational Safety and Health, with the responsibility of conducting and funding research into exposure hazards and recommending safety standards. The act also established OSHA, the Occupational Safety and Health Administration, which, after due procedure, would enact into law and then enforce NIOSH recommended standards (6).

NIOSH Recommendations

NIOSH funded a number of surveys, including the National Survey of Occupational Disease among OR Workers, conducted in conjunction with the American Society of Anesthesiologists (ASA) Ad Hoc Committee on Waste Anesthetic Gases. This health survey covered 49,000 potentially exposed and 26,000 unexposed personnel (7). The results, published in 1974, showed an increased reported incidence among women of spontaneous abortions, liver and kidney disease, and cancer, and a higher reported incidence of congenital abnormalities in the offspring of exposed women. In exposed men, cancer incidence did not increase but hepatic disease incidence did.

NIOSH sponsored further related studies, including investigations of the effects of waste vapors on perceptual skills (8, 9) and of methods for reducing exposure to waste gases (10).

In March 1977, NIOSH published *Criteria for a Recommended Standard—Exposure to Waste Anesthetic Gases and Vapors* (11). This report estimated that 214,000 workers were potentially exposed on a day-to-day basis to trace anesthetic gases. The document reviewed all the available data and found that, though not completely definitive, the evidence strongly suggested a relationship between health hazards and trace concentrations of anesthetic gases. No cause-effect relationship was established and no safe exposure levels could be identified. However, the document recommended that risks should be minimized as much as possible by maintaining "exposures as

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low as is technically feasible." The document also recommended measures to reduce exposure, monitor exposure levels, and improve record-keeping.

NIOSH recommended environmental limits for the upper boundary of exposure as follows (11):

> Occupational exposure to halogenated anesthetic agents shall be controlled so that no worker is exposed at concentrations greater than 2 parts per million (ppm) of any halogenated anesthetic agent. .... When such agents are used in combination with nitrous oxide, levels of the halogenated agent well below 2 ppm are achievable. In most situations, control of nitrous oxide to a time-weighted average (TWA) concentration of 25 ppm during the anesthetic administration period will result in levels of approximately 0.5 ppm of the halogenated agent.
>
> Occupational exposure to nitrous oxide when used as the sole anesthetic agent, shall be controlled so that no worker is exposed at TWA concentrations greater than 25 ppm during anesthetic administration. Available data indicate that with current control technology, exposure levels of 50 ppm, and less for nitrous oxide are attainable in dental offices.

These limits were based on two pieces of work, namely that of Whitcher et al in 1975 (10), who showed that these restricted levels were readily attainable in the operating room when certain precautionary measures were taken, and the work of Bruce and Bach (12), who found no decrement in the psychomotor capacities of volunteers exposed for four hours at these levels.

To get a perspective on what ppm (parts per million) means, the presence of 25 ppm of N_2O in the atmosphere represents a concentration of 1/400 of 1%!

What kinds of levels of trace anesthetics may be found in the operating room? When no attempt has been made to reduce leakage of or to scavenge waste gases, trace gas levels of 400–600 parts per million of nitrous oxide and from 5 to 10 parts per million of halogenated agents may be detected (13). Effective scavenging alone can reduce these levels more than tenfold (14).

Optimum reduction of air contamination is achieved by certain control measures supported by an air monitoring program. The monitoring is essential and ensures the efficacy of control measures; the identification of leaks or defects in technique; and documentation of compliance with the recommended standard.

NIOSH recommends that monitoring be done by a knowledgeable person familiar with techniques of sampling, or by an industrial hygienist (11). Monitoring requires both sampling and analysis. Analysis may be performed by infrared methods or gas chromatography, either in or outside the hospital.

Sampling Methods

Sampling has two aspects: where to do it, and when to do it.

Where to Sample. Monitoring personal exposure is not required by the NIOSH recommended standard (11), although perhaps it offers the most pertinent information on individual exposure. Sampling in the immediate work area of the most highly exposed person—the anesthesiologist—is recommended. A recent study (15) has shown that measuring N_2O at the anesthesia-machine shelf level correlates well with personal sampling when levels of N_2O are below 35 ppm (15). Shelf-level measurement is certainly more practical than personal sampling.

General area sampling is valid if complete air mixing in the operating room has been previously demonstrated. In a room where all leakage is under effective control, gas concentrations may be uniform, making this kind of sampling appropriate.

When to Sample. The timing of sampling is also critical in obtaining representative exposure concentrations. There are essentially three types of temporal sampling: grab, time-weighted average (TWA), and continuous sampling.

Grab sampling is useful for monitoring steady-state conditions, such as high-pressure leakage from nitrous oxide lines, which produces baseline nitrous oxide levels. With this technique, an air sample from the empty operating room is taken for subsequent analysis. Inert containers are available for this purpose from Boehringer Laboratories (Wynnewood, Penn). The container is sealed and mailed to the company, which analyzes the contents. Delay in obtaining the results is one obvious disadvantage. Also, since anesthetic leakage tends to be intermittent, the value of such sampling is limited.

The time-weighted average (TWA) sample is obtained by pumping ambient air continuously into an inert bag at a constant low flow rate, usually around four liters an hour. The bag has a capacity of 20–30 liters. The resulting concentration in the bag therefore represents an average exposure over the collection period.

Time-weighted average gas sampling systems are commercially available and provide TWA concentrations over periods of one to eight hours. The sampling pump can be mounted on an intravenous pole. Aliquots of a collected TWA sample may be analyzed in house or mailed in the inert containers used in grab sampling to a central testing laboratory. The time-weighted average for personal exposure may also be obtained from a battery-powered sampling pump and collection bag worn by the anesthesiologist.

Knowledge of the time-weighted average concentrations is useful for documentation purposes, since the recommended standard refers to a TWA concentration of 25 parts per million, although the time period for collection is not specified (11).

The Infrared Analyzer. The portable infrared analyzer, which is capable of continuous sampling, is the most useful method for monitoring OR atmosphere. This device offers a continuous readout, so it can be used for the detection of leaks, demonstration of anesthetic technique errors, and determination of pollution levels. Analyzers operate on the principle that most gases present unique infrared absorption spectra. For example, the infrared absorption spectrum for nitrous oxide has a peak at around 4.5 microns (14).

These infrared analyzers work as follows. A pump perfuses a cell with OR air. The infrared source generates a light beam which is filtered to pass the infrared component at around 4.5 microns, to test for nitrous oxide. The beam is transmitted through the sample cell and is sensed by a detector. The higher the concentration of nitrous oxide, the more the absorbance of infrared radiation and the less the energy at the detector. The signal is processed and displayed in parts per million N_2O. Infrared analysis can detect concentrations in parts per 100 million.

Infrared analyzers can also measure trace concentrations of halogenated agents, although they are less reliable for this purpose since these agents have overlapping absorption spectra.

Using a chart recorder connected to the analyzer, a continuous tracing of the nitrous oxide concentration in room air can be obtained during anesthesia. The value of this kind of monitoring is quite obvious. One can see any instantaneous peaks reflecting a high level of the gas, such as may be due to adjustment of a face mask. Or the chart may alert one to a leak in some other part of the system. Also, since waste-gas levels do fluctuate, this approach is more reliable than a grab sample in measuring concentrations that may be inhaled by OR personnel.

Time-weighted average concentrations may be obtained from the infrared analyzer by integrating the output—determining the area under the curve and dividing by the time. This can be done by counting the squares or using a planimeter. The integration for nitrous oxide can also be derived electronically, using a microcomputer. This provides a continuously updated TWA concentration and is relatively inexpensive. If a peak concentration suggestive of a leak in the system is sensed, the source of the leak can be "sniffed out," using the analyzer as a leak detector.

The ideal air-monitoring program should measure all anesthetic gases employed in the operating room. The recommended standard, however, requires monitoring only of the most frequently used agent, since recommended work practices and control procedures will reduce all agents proportionately (11, 14). Thus, nitrous oxide can be monitored and acts as a tracer for the potent agents that may be administered along with it in some fixed proportion, usually 50:1.

The Passive Diffusion Monitor. A new approach to monitoring OR pollution was introduced relatively recently in the form of passive diffusion monitors; the Nitrox dosimeter is an example (R. S. Landauer Co., Illinois). While this device is designed for monitoring personal exposure, it could also be used for area sampling. In concept, the device is similar to the radiation badges worn by personnel in x-ray departments to monitor their exposure to radiation. The dosimeter is a tube which contains a molecular sieve that traps nitrous oxide. The tube is worn by the person being tested and must be uncapped at the beginning of the period of exposure to nitrous oxide and capped at the end. It is designed to sample over a period of 40 hours, and the wearer must keep a record of the exposure time. The effective air sampling rate is about 5 cc per hour. The dosimeter, labelled with the individual's name and period of exposure, is returned to the company for analysis. Results are expressed in TWA form, ppm-hours. These dosimeters are remarkably accurate and when tested against continuous TWA sampling using an infrared analyzer, they show a correlation coefficient of close to 1.0.

Ideal Monitoring and Current Practice

How frequently should the operating room be monitored? The recommended standard (11) requires repetitive sampling quarterly in locations in which mixed inhalation anesthetic agents are used and whenever ventilation, anesthetic equipment, or scavenging techniques are modified. Ideally, monitoring should be performed quite frequently, even continuously, but continuous monitoring is impractical and very expensive.

Empty operating rooms, out of use for at least two hours, should be surveyed to detect background leakage from equipment high-pressure systems. The rooms should be resurveyed later in the day and while in use to detect actual working exposure levels.

If high levels are detected, some explanation should be sought and remedial action taken as soon as possible and documented. High levels intraoperatively may, however, represent an unavoidable sequela of the anesthetic technique in use at the time of monitoring.

Incidentally, although anesthestiologists are the ultimate monitors of the patient in the operating room, their senses are not very effective at protecting themselves against trace anesthetic concentrations. The olfactory thresholds for nitrous oxide and halothane are 10%–30% (100,000–300,000 ppm) and 50–100 ppm, respectively (16). The nose is very sensitive to the smell of methoxyflurane (Penthrane) and can detect 0.1–2 ppm of this agent, but this anesthetic is now rarely used.

No Legal Requirements. At present, there are no formal requirements for monitoring the OR atmosphere for waste anesthetic gases, there are only recommendations (17). The NIOSH-recommended limits have not yet been enacted into law by OSHA, and it is quite likely that they never will be. Such a law has been opposed by both hospitals and anesthesiologists because the recommendations are considered by many to be unreasonable, for several reasons.

First, the recommended limits are based upon the work of Whitcher et al in 1975, who maintained that these levels were readily achievable (10); but this was subsequently shown not to be true by Whitcher himself (18). In 1979, he reported data to the effect that even when all reduction measures were taken, exposure levels depended very much on the anesthetic technique used. Thus, when using a mask, mean levels of 180 ppm N_2O were found. When the patients were intubated, mean levels of 16 ppm were achieved. Should we therefore intubate all our patients to keep to this arbitrary level? Obviously not. Clearly each technique has its associated degree of contamination. A steal induction of a pediatric patient would certainly violate the standard, yet it has obvious advantages for the patient.

Second, the results of tests of psychomotor activity conducted by Bruce and Bach (12), which also formed a basis for the standard, have not been substantiated by other workers, all of whom found no effects at much higher trace anesthetic levels (19, 20).

Third, no "safe" trace level has ever been demonstrated for any of the anesthetics in use.

How Hazardous Are Trace Levels? An even more fundamental issue still remains unresolved. Are trace levels of anesthetics really hazardous? Certainly no cause-effect relationship has ever been demonstrated (11, 21, 22). The studies to date which have incriminated anesthetics have all been based on questionnaire surveys sent to people who were assumed either to have been exposed to trace anesthetics in the operating room, or not to have been so exposed. Such studies are notoriously unreliable. They are wide open to responder bias, and such bias may explain all of the observed differences to date between exposed and unexposed personnel (22).

That such bias exists in these studies was very clearly demonstrated by Axelsson and Rylander (23). They studied a total of 655 pregnancies among workers in one Swedish hospital. Starting with a postal survey, they then checked the accuracy of the responses they received against medical records. They found that all women suffering miscarriages who worked at sites with exposure to anesthetic gases reported their work sites and miscarriages, whereas one third of all miscarriages by women who were not so exposed during pregnancy went unreported in the questionnaire. The authors concluded that their study draws attention to the methodologic difficulties in using questionnaires to study pregnancy outcome and pinpoints especially the importance of the response bias.

Further epidemiologic investigations are clearly necessary to establish whether or not trace concentrations of anesthetics are hazardous. The ASA Ad Hoc Committee recently retained a group of epidemiologists and statisticians to review all the available data pertaining to health hazards among OR workers. Their report (24), the "Epistat" report, urged that future studies be "prospective cohort studies, with careful documentation of type, amount and duration of exposure, meticulous and uniform follow-up and thorough ascertainment and confirmation following pre-defined criteria, of outcome events." This is to avoid previous methodological errors. The report also found that the only consistently reported health hazard was an increased relative rate of spontaneous abortion.

The authors observed that, on the basis of the available data, the relative risk for spontaneous abortion among exposed women is approximately 33% greater than for nonexposed women. The authors further stated that the magnitude of this increase is well within the range that might be due to bias or uncontrolled confounding variables, and that the epidemiologic data currently available are insufficient for developing standards or setting exposure limits. Even if this increased relative risk were true, it should be viewed in perspective. Thus, maternal smoking of one pack of cigarettes per day increases the spontaneous abortion rate by 80%, and maternal consumption of alcohol may increase the rate by 200%!

Current Goals. To date, trace concentration of anesthetics have neither been fully incriminated nor fully exonerated as causes of the reported health problems in OR workers. However, absence of evidence does not constitute evidence of absence, and while the possibility of a hazard does exist, measures should be continued both to reduce exposure and to monitor the effects of these measures. This is certainly recommended by all concerned agencies, including NIOSH, The American Hospital Association, the Joint Commission on Accreditation of Hospitals, and the American Society of Anesthesiologists (ASA). The ASA Ad Hoc Committee on Effects of Trace Anesthetic Agents on Health of Operating Room Personnel emphasizes that the administration of anesthesia and the safety of the patient are our primary goals, and that pollution control must be of secondary concern (25).

Further studies are necessary to resolve the question of whether anesthetics are pollutants; the answer may well never be known. Meanwhile the subject remains up in the air.

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Continuous Monitoring of Mixed Venous Oxygen Saturation in Clinical Practice

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Abstract

The saturation of hemoglobin with oxygen in mixed venous blood depends on cardiac and respiratory factors along with tissue oxygen consumption. Continuous monitoring of mixed venous oxygen saturation is now possible with the fiberoptic reflectometry system. Such monitoring is of value in the care of critically ill patients as an indicator of trends in cardiorespiratory function and of the response to therapeutic maneuvers designed to increase oxygen delivery to the tissues.

The delivery of oxygen to the tissues is dependent upon cardiac and pulmonary factors and is expressed in the following relationship:

$$\text{Oxygen delivery} = \dot{Q}_t \times CaO_2 \text{ ml/minute}$$

where $\dot{Q}_t$ is the cardiac output in liters/minute and CaO_2 is the arterial oxygen content in ml/liter.

CaO_2 is the product of the saturation of hemoglobin with oxygen (SaO_2) and the arterial oxygen tension (PaO_2) expressed as follows:

$$CaO_2 = (SaO_2 \times Hb \times 1.34) + (0.0031 \times PaO_2) \text{ ml/dl}$$

where Hb is the hemoglobin concentration in gm/dl, 1.34 is the amount of oxygen combining with 1 gm of hemoglobin, and 0.0031 is the amount of oxygen in solution in the blood for each millimeter of Hg partial pressure.

The Fick equation describes the relationship between the cardiac, pulmonary, and tissue factors affecting oxygen transport and utilization. It can be written as follows:

$$C_{\bar{v}}O_2 = CaO_2 - (\dot{V}O_2/\dot{Q}_t)$$

where $C_{\bar{v}}O_2$ is the oxygen content in mixed venous blood in ml/liter and $\dot{V}O_2$ is the tissue oxygen uptake expressed in ml/minute. This equation demonstrates that $C_{\bar{v}}O_2$ is directly proportional to CaO_2 and $\dot{Q}_t$, but indirectly proportional to VO_2. As the amount of oxygen in solution in mixed venous blood is relatively minor, the last equation can be rewritten in terms of saturation as follows:

$$S_{\bar{v}}O_2 = SaO_2 - [\dot{V}O_2/(\dot{Q}_t \times Hb \times 1.34)]$$

$S_{\bar{v}}O_2$ is the saturation of hemoglobin with oxygen in mixed venous blood expressed as a percentage. Thus, $S_{\bar{v}}O_2$ is influenced by cardiac factors ($\dot{Q}_t$), pulmonary factors (SaO_2), tissue oxygen uptake (VO_2), and hemoglobin concentration. If tissue oxygen uptake is constant, $S_{\bar{v}}O_2$ reflects alterations in cardiac output and arterial oxygen saturation. This circumstance is frequently present in the operating room during general anesthesia and neuromuscular blockade.

In the clinical setting, baseline information regarding cardiopulmonary function can be obtained by the determination of cardiac output using the thermodilution technique and by the analysis of arterial blood gas tensions. On the background of these data, alterations in $S_{\bar{v}}O_2$ can then be interpreted if the changes in cardiopulmonary function are not occurring rapidly. It is for this reason that, until recently, intermittent measurement of $S_{\bar{v}}O_2$ has not played a major role in patient management. Thus, an important step in monitoring was achieved when the technology became available for the continuous measurement of mixed venous oxygen saturation.

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The Fiberoptic Reflectometry System

Previous studies have described in vivo continuous monitoring of $S_{\bar{v}}O_2$ by fiberoptic reflectometry. The method was introduced as a promising tool in various clinical situations, including diagnostic cardiac catheterization (1, 2) and intra-operative and postoperative monitoring in cardiac surgery (3, 4). Technical problems, however, delayed clinical investigation and the widespread use of the technique. These problems included catheter stiffness, lack of thermodilution cardiac output determination capability, difficult standardization, need for frequent recalibration, and fibrin deposits on the tip of the catheters.

A new fiberoptic reflectometry system (Oximetrix, Mountain View, California) connected to a thin umbilical catheter has been described and evaluated in neonates (5). The instrument was found to be accurate, easy to standardize, and reliable over long periods of time. Its rapid response time allowed its use as a guide for oxygen therapy and assisted ventilation. This system has been coupled to a new pulmonary arterial flow-directed catheter (Oximetrix; Opticath) combining the fiberoptic reflectometric system for continuous display of $S_{\bar{v}}O_2$ with the capacity for hemodynamic measurements including thermal dilution cardiac output estimation.

The system consists of light-emitting diodes which generate alternating pulses of three different wavelengths (between 600 and 1,000 nm) 244 times per second. The light is generated by an optic module which is attached to the hub of a newly developed pulmonary arterial catheter. The light travels through a fiberoptic channel in the catheter to its tip where it is absorbed, refracted, and reflected by the red blood cells in the pulmonary artery. A second fiberoptic channel conducts the reflected light to a photodetector. Blood reflectance changes with variations in its colored constituents (hemoglobin, oxyhemoglobin, carboxyhemoglobin, sulphemoglobin, and methemoglobin).

The oxygen saturation of hemoglobin is derived from the relative intensities corresponding to the three different wavelengths. The bedside oximeter provides a digital readout of the average value for $S_{\bar{v}}O_2$ of the preceding 5 seconds. This value is updated every second. A two-speed paper recorder allows further analysis of changes in saturation. Audible and visible alarms warn when light intensity varies. This may happen when the tip of the catheter faces a vessel wall, is in the wedge position, or is covered with fibrin deposits, or when the fiberoptics are damaged.

The catheter is $7^1/_2$ French in diameter and is constructed of flexible polyvinyl chloride, to which has been added aramid fibers to protect against excessive distortion. The catheter contains a distal (pulmonary arterial) and a proximal (right atrial) lumen for pressure monitoring, blood sampling, or fluid injection. A thermistor is located approximately 3 cm from the tip and a 1.5 ml inflatable balloon is at the extremity. Two fiberoptic channels provide in vivo reflectometry. The system is calibrated either before insertion by using a reference surface supplied with the catheter or after insertion by adjustment to $S_{\bar{v}}O_2$ determinations made by a reliable laboratory co-oximeter on pulmonary arterial blood samples.

Catheter insertion is accomplished by the conventional technique utilizing jugular, subclavian, or cubital venous access. The correct position of the catheter in the pulmonary artery is assessed by pressure waveform monitoring and confirmed by chest radiography. A continuous infusion of heparinized normal saline solution (4 ml/hour) is used to prevent occlusion of the catheter lumina.

The accuracy and reliability of the system have been demonstrated by comparing values of $S_{\bar{v}}O_2$ obtained from the reflectometer system with values obtained from a laboratory co-oximeter (6). These in vivo and in vitro values of $S_{\bar{v}}O_2$ show a good correlation and there is an alteration of less than 1% of saturation for each 24 hours the catheters are in place. This drift is negligible if a daily recalibration procedure is followed.

The accuracy of the system does not depend upon the method of calibration, the hemoglobin concentration, the body temperature, or the cardiac index. The ease and success of placement of these catheters does not differ from the results obtained with nonfiberoptic catheters and the occurrence of dysrhythmias during passage through the right atrium and right ventricle is not increased.

Clinical Applications

The degree of saturation of hemoglobin with oxygen in mixed venous blood is an indicator of arterial oxygen content, of cardiac output, and of peripheral tissue utilization of oxygen. Oxyhemoglobin saturation also depends on the shape of the oxyhemoglobin dissociation curve which reflects the hemoglobin affinity for oxygen, the latter varying with pH, arterial carbon dioxide tension, temperature, and the level of 2,3 diphosphoglyceric acid in erythrocytes. Mixed venous oxygen saturation thus reflects pulmonary and cardiac function, tissue blood flow, and oxygen consumption.

Because the oximetry system provides continuous, rapid response to changes in $S_{\bar{v}}O_2$, there are many situations during the care of patients with actual or impending cardiorespiratory failure for which continuous monitoring of $S_{\bar{v}}O_2$ is of value.

Cardiac Output. Mixed venous oxygen saturation and cardiac ouput are directly proportional, providing that SaO_2, Hb, and $\dot{V}O_2$ remain constant. This is an ideal situation and the closest to it, in the clinical field, is perhaps represented by the patient undergoing general anesthesia and neuromuscular blockade. The other extreme is represented by the apprehensive patient with respiratory failure who is struggling against the activities of a mechanical ventilator (increased $\dot{V}O_2$). Bearing in mind these factors, the effect of various disease processes, for example infarction, on myocardial function can be observed by monitoring $S_{\bar{v}}O_2$. As myocardial function fails and oxygen extraction ($C_{a-\bar{v}}O_2$) increases, $S_{\bar{v}}O_2$ will decrease. A value below 60% indicates inadequate oxygen delivery to supply tissue requirements. A value below 50% indicates the commencement of anaerobic metabolism and lactic acidosis.

Pulmonary Oxygen Transfer. In the absence of myocardial dysfunction, as CaO_2 decreases due to ventilation/perfusion mismatching in the lungs, the cardiac output increases. If oxygen consumption during this process remains stable, $S_{\bar{v}}O_2$ will decrease when cardiac output is no longer able to compensate for a decrease in CaO_2. Thus, by following $S_{\bar{v}}O_2$ and indicators of cardiac function, an assessment of respiratory gas exchange can be made and used to demonstrate the immediate response to alterations in the extent and mode of mechanical ventilatory support.

Oxygen Consumption. Under steady-state conditions, oxygen delivery ($CaO_2 \times \dot{Q}_t$) to the tissues should be sufficient to satisfy tissue demands and the arteriovenous oxygen content difference should remain normal at 5 ml/100 ml of blood. However, if tissue oxygen demand suddenly increases, as with the onset of muscular exercise, oxygen extraction will initially increase and $S_{\bar{v}}O_2$ will decrease. As compensation, $\dot{Q}_t$ will increase, oxygen delivery will increase, and $S_{\bar{v}}O_2$ will return to the normal value of 75%. In the absence of an added oxygen supplement, only minimal pulmonary compensation is possible, and $S_{\bar{v}}O_2$ thus provides an indicator of cardiac compensation for increased oxygen consumption.

Sepsis. In the early stages of septicemia, bacterial endotoxin alters cellular metabolism and decreases tissue oxygen utilization. Thus, tissue oxygen extraction decreases while tissue blood flow increases due to peripheral vasodilatation. The end result is comparable to a peripheral left-to-right shunt and results in a rise in $S_{\bar{v}}O_2$. This may be the first clinical indicator of the onset of septicemia. The effects of sepsis on cellular metabolism are comparable to those of cyanide poisoning which has been shown to produce an increase in $S_{\bar{v}}O_2$ (7). As part of the pathophysiological response to sepsis, there is an increase in $\dot{Q}_t$, further increasing oxygen delivery to tissues whose oxygen requirements have decreased. In the latter stages of sepsis, cardiac function and $S_{\bar{v}}O_2$ decrease, indicating a worsening prognosis.

Best Positive End-Expiratory Pressure. The concept of best or optimum positive end-expiratory pressure (PEEP) suggests that a particular level of positive pressure applied throughout the respiratory cycle results in improved oxygen delivery to the tissues (8). However, beyond a certain level of PEEP, cardiac and pulmonary side-effects dominate and oxygen delivery decreases. For a given circulating blood volume, as PEEP is increased, oxygen delivery ($\dot{Q}_t \times CaO_2$), as indicated by $S_{\bar{v}}O_2$, increases up to the point where the unwanted side-effects occur. This point has been called best PEEP and can be quickly determined by noting the effect of incremental PEEP on $S_{\bar{v}}O_2$. This method, which does not require multiple determinations of arterial blood gas tensions and $\dot{Q}_t$, is beneficial in decreasing the cost of respiratory care.

Control of Inotropic, Pressor, and Dilator Therapy. In the patient with stable oxygen consumption and pulmonary oxygen transfer, manipulations of cardiac inotropes, vasopressor, and vasodilator agents can be closely followed by changes in $S_{\bar{v}}O_2$. Titration of these agents can produce immediate responses in $S_{\bar{v}}O_2$ long before cardiac output estimations can be made and estimations of vascular resistance derived; for example, an increase in the rate of an infusion of dopamine, in an otherwise stable patient, will produce an increase in $S_{\bar{v}}O_2$ if cardiac output is increased. Similarly, an inappropriate administration of sodium nitroprusside will rapidly produce a decrease in $S_{\bar{v}}O_2$ long before the change in peripheral resistance can be calculated.

Hemodynamic and Respiratory Monitoring. By adjusting the high and low alarm limits for saturation on the bedside oximeter, the $S_{\bar{v}}O_2$ monitor can provide early warning of impending cardiac arrest or advancing respiratory failure. A decrease in $S_{\bar{v}}O_2$ below 60% indicates the need for investigation of the cause, which should include an estimation of cardiac output by the thermodilution capability of the catheter and an analysis of arterial blood gas tensions. If the decrease in $S_{\bar{v}}O_2$ is rapid, time for such measurements may not be available. Therapy must be empirical and the oximeter system will indicate its success or failure.

Conclusions

The oximeter system is a valuable, accurate, and reliable indicator of the effects of therapeutic maneuvers on cardiopulmonary function and is a useful warning system for deterioration in these functions. It is a device which helps the physician caring for critically ill patients to determine the best approach to therapy for acute cardiorespiratory failure and then provides a rapid indication of the success or otherwise of such therapy. These features characterize a monitoring system that is of value in the care of the critically ill patient in the operating room and the intensive care unit.

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Intraoperative Esophageal Electrocardiography

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ABSTRACT

Complex dysrhythmias in anesthetized patients can pose difficult diagnostic problems to the anesthesiologist. Although the conventional surface electrocardiogram (ECG) is now a standard intraoperative monitor, lack of distinct P waves (atrial depolarization) often hinders dysrhythmia interpretation. Esophageal electrocardiography has been shown to be a useful technique for dysrhythmia analysis in nonsurgical patients, and we have recently studied its value during cardiac surgery. The appearance of distinct P waves on the esophageal ECG was shown to facilitate accurate dysrhythmia diagnosis in the operating room. The esophageal ECG also appears to be useful for the detection of subendocardial ischemia; however, its value as a monitor of posterior ventricular ischemia is controversial. With the commerical availablity of an esophageal stethoscope with ECG capabilities, esophageal electrocardiography can now be routinely and safely practiced in the operating room, provided that standard electrical-safety precautions are followed.

The development of complex dysrhythmias in anesthetized patients is frequently associated with hemodynamic compromise. Since prompt and accurate dysrhythmia analysis facilitates the institution of proper antiarrhythmic therapy, intraoperative electrocardiography has become a valuable monitor to the anesthesiologist. Unfortunately, however, the conventional surface electrocardiogram (ECG) is not always sufficient for definitive dysrhythmia diagnosis (1–3).

Dysrhythmia diagnosis necessitates a clear interpretation of the temporal sequence of atrial and ventricular depolarization and therefore requires the electrocardiographic inscription of distinct P and QRS wave forms. While depolarization of the relatively large ventricular mass results in a distinct QRS complex, depolarization of atrial tissue often produces inappreciable P wave deflections on the surface ECG. This inability to determine accurately the temporal relationship between P waves and QRS complexes frequently hinders dysrhythmia analysis.

Anatomic Relationships. Esophageal electrocardiography has been proven to be a useful technique for determining the sequence of atrial depolarization (2–9). The extreme sensitivity of the esophageal lead for detecting atrial contractions is based upon the principles of the exploratory lead, developed by Wilson in the 1930s (10, 11). Wilson demonstrated that the amplitude of cardiac electrical potentials rapidly diminishes as it spreads through the body away from the heart and that when an exploring electrode is in close proximity to the heart, it becomes almost as sensitive as a direct epicardial lead for detecting cardiac electrical events. The esophagus provides a relatively noninvasive avenue for advancing an electrocardiographic lead into close proximity with the heart. Thus, an appreciation of the anatomic relationship between the esophagus and the various cardiac structures is necessary for an understanding of the specific electrical events accentuated by esophageal electrocardiography.

The distal half of the esophagus lies immediately posterior to the heart. Interposing structures are solely comprised of esophageal wall, connective tissue attachments, and pericardium. Left atrial tissue is most closely applied to the esophagus, and normally an esophageal lead can

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be positioned 0.5 to 1.0 cm from the left atrium (11–13). In the distal esophagus, superior to the diaphragm, the posterior aspect of the left ventricle is immediately ventral to the esophagus (13). Furthermore, unlike the relatively proximal precordial leads, which are partially insulated from the heart by poorly conducting lung tissue, the esophageal leads are separated from the heart by tissue which has excellent electrical conducting characteristics (11).

Unipolar esophageal electrocardiograms demonstrate potential curves dependent upon the position of the lead within the esophagus. If the esophageal lead electrode is located above or below the level of the left atrium (approximately less than 30 cm or greater than 45 cm, nares to electrode), the P wave takes on the characteristics of a low amplitude P wave similar to that seen with the surface ECG (13). When the esophageal electrode is directly behind the left atrium (approximately 30–45 cm, nares to electrode), the P wave primarily reflects the electrical currents generated by adjacent atrial tissue (13). The wave amplitude increases because of proximity to the atrium, and the waveform inscribes a sharp, intrinsic deflection (11, 14). As atrial depolarization approaches the electrode, the upstroke of the P wave is inscribed; this abruptly reverses to a downstroke as the depolarization front spreads away from the electrode (11, 14) (Fig. 1).

The Bipolar Lead. Although the esophageal ECG was first introduced as a unipolar lead, bipolar esophageal electrocardiography has subsequently been found to be advantageous for dysrhythmia analysis (2–4). The bipolar esophageal ECG depicts the difference in potential between the two esophageal electrodes. When placed behind the left atrium, the bipolar lead, as compared to the unipolar lead, results in a larger P:QRS ratio. This prevents camouflage of the P wave by a simultaneous QRS. In fact, the QRS complex can be of such low amplitude, that a simultaneous surface ECG has been recommended to determine the sequence of ventricular depolarization (2). Also, the bipolar esophageal ECG is an extremely sensitive indicator of changes in the pattern of atrial arrhythmias, so that atrial ectopic beats are easily distinguished from normal sinus rhythms (2, 4).

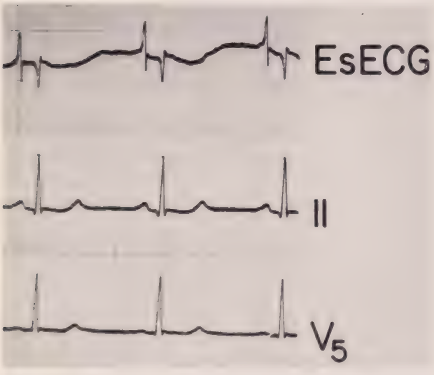

Fig. 1. Prominent biphasic P wave in esophageal ECG is contrasted with simultaneous recordings from conventional leads II and V5 from patient in normal sinus rhythm.

Esophageal ECG as Monitor. Several studies have demonstrated the superiority of the esophageal ECG over the conventional surface ECG for dysrhythmia diagnosis in nonsurgical patients (2–8). I and my colleagues recently evaluated the esophageal lead as an intraoperative electrocardiographic monitor in 20 patients undergoing cardiac surgical procedures (9).

Two esophageal leads were incorporated into a modified 24-French esophageal stethoscope. The external chloridized silver-wire electrodes were located 7 and 20 cm from the distal end of stethoscope and connected as right and left arm electrodes of a lead I ECG, thus establishing a bipolar esophageal ECG circuit. The ECG monitor was electronically isolated and an electrocautery protection filter (HP 14392A) was inserted into the esophageal ECG circuit. The modified esophageal stethoscope was placed by the anesthesiologist in the usual manner and then positioned so that the bipolar esophageal leads produced a maximum P wave amplitude on ECG. Conventional surface ECG leads II and V5, as well as the esophageal ECG, were continuously monitored during the operation. Definitive dysrhythmia analysis was difficult using either lead II or V5; correct diagnosis was achieved in 53.8% of cases using lead II and 42.3% of cases using V5. However, the inscription of large, distinct P waves on the bipolar esophageal ECG clearly indicated the sequence of atrial and ventricular depolarization. Accuracy of dysrhythmia analysis was increased such that 100% of the dysrhythmias were correctly diagnosed.

The superiority of the esophageal lead over lead II and V5 for dysrhythmia analysis is demonstrated in Figures 2–4. The progression of atrioventricular heart block from first-degree to second-degree Mobitz type II can be clearly detected on the esophageal ECG (Fig. 2). However,

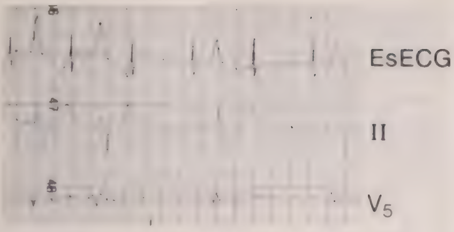

Fig. 2. Top left Progression of heart block from first-degree atrioventricular block to second-degree Mobitz type II can be clearly detected from esophageal ECG. In leads II and V5, P waves are hidden in downslope of preceding T waves. Modified from Anes Analg 1982; 61:781–785.

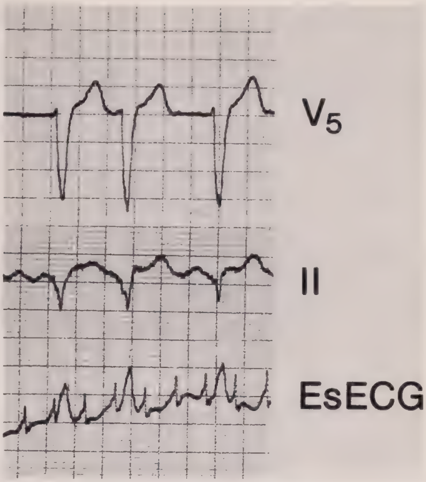

Fig. 3. Top right Conventional leads V5 and II suggest diagnosis of atrial fibrillation. However, simultaneous esophageal ECG clearly depicts atrial flutter waves at a rate of $280 \cdot \text{min}^{-1}$ with varying atrioventricular block. Reprinted with permission of the International Anesthesia Research Society, from Anes Analg 1982; 61:781–785.

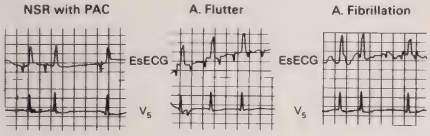

Fig. 4. Bottom left Esophageal ECG distinctly depicts dysrhythmia progression from normal sinus rhythm (NSR), with one premature atrial contraction (PAC) to atrial flutter (A. Flutter), and atrial fibrillation (A. Fibrillation). Simultaneous V5 lead does not reflect these major alterations in atrial rhythm. Reprinted with permission of the International Anesthesia Research Society from Anes Analg 1982; 61:781–785.

in leads II and V5, P waves are hidden in the downslope of preceding T waves. Also, the obvious atrial flutter waves in the esophageal ECG corrected a misdiagnosis of atrial fibrillation which was made after observing leads II and V5 (Fig. 3). The degeneration of an atrial rhythm pattern from sinus rhythm with a premature atrial contraction to atrial flutter and then atrial fibrillation can be distinctly recognized from the esophageal ECG (Fig. 4), while the intraoperative V5 lead is practically unaffected by these major rhythm changes. This study demonstrated the value of an intraoperative esophageal ECG for dysrhythmia analysis.

The ability of the esophageal lead to detect ventricular ischemia has been evaluated (11, 15–18). Its usefulness as a monitor of ventricular lesions, however, is controversial. The QRS complex varies greatly depending upon the anatomic relationship of the esophageal lead to the cardiac chambers. Esophageal electrocardiograms recorded from the level of the left atrium have been shown to depict left ventricular cavitary potentials (11, 16). The esophageal lead at this level is electrically linked to the left ventricular cavity by a low resistance pathway consisting of the intra-atrial and ventricular blood volume (11). With normal depolarization patterns progressing from endocardium to epicardium, the ventricular complex from an esophageal lead at the atrial level inscribes a QR or QS pattern. Subendocardial ischemia has been shown to be clearly depicted by elevation of the RS-T segment, recorded from the esophageal lead at the atrial level (15). During our intraoperative study, we detected evidence of ventricular ischemia by an elevation of RS-T segments on the esophageal ECG while leads II and V5 remained unchanged (Fig. 5). At the infra-atrial level, the esophageal lead is posterior to the left ventricle and should be a valuable monitor for the detection of true posterior ischemia and infarction. This has not proven to be the case, however, probably because correct placement of the esophageal lead directly posterior to the left ventricle is difficult (16–18). Intracavitary Q waves appear if the lead is not low enough and, if positioned too low, the esophageal lead depicts the diaphragmatic surface of the left

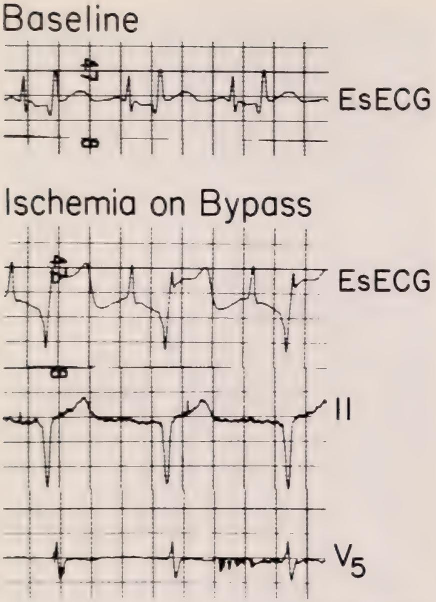

Fig. 5. Evidence of ventricular ischemia by RS-T segment elevation at conclusion of cardiopulmonary bypass appears on esophageal ECG (EsECG) only. Also, distinct P waves evident on EsECG are not detectable on leads II and V5. Modified from Anes Analg 1982; 61:781–785.

ventricle, providing no more information than aVF (18). Therefore the esophageal lead appears to be sensitive for detecting subendocardial ischemia but may not be advantageous for monitoring true posterior ischemia.

Methods of Use. Intraoperative esophageal electrocardiography definitely advances the ability of the anesthesiologist to analyze complex dysrhythmias and is a sensitive technique for detecting subendocardial ischemia. Presently, with the commercial availability of an esophageal stethoscope with ECG monitoring capabilities (Cardio-Esophascope, Portex, Wilmington, Mass), esophageal electrocardiography can be routinely and safely practiced in the operating room. Electrical safety precautions must always be strictly followed by using electrocardiographic equipment which is electrically isolated and adheres to the standards of the American Heart Association (19). Further protection is provided by inserting an electrocautery protection filter (Hewlett Packard No. 14392A) into the ECG circuit. A bipolar esophageal ECG can then be constructed by inserting the two esophageal lead wires into a right and left arm terminal of a lead I ECG circuit, and a unipolar esophageal ECG can be structured by inserting the single esophageal lead wire into a right arm terminal of an aVR circuit. This esophageal stethoscope with ECG capabilities can also be applied to unconscious patients in the recovery room and in intensive care units.

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Pulmonary Artery Catheterization: Past, Present, and Future

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The era of cardiac catheterization in humans began in 1929 when Werner Forsmann, a 25-year-old surgical resident, exposed a vein in his own left arm and advanced a urethral catheter into his venous system (1). Using a mirror and fluoroscopy, he followed the catheter's progress into his right atrium. He then climbed a few stairs to the x-ray department and documented the event by means of a chest x-ray.

After Forssman's self-inflicted experiment, the study of the human cardiovascular system by means of invasive techniques became widespread (1).

Past

The first mention of the pulmonary artery wedge position dates back to 1947. Dexter and his colleagues, while studying congenital heart disease, noted that the pressure obtained with the catheter in the pulmonary artery wedge position accurately reflected the pulmonary venous and left atrial pressure (2). The early catheters, however, were very stiff and difficult to manipulate. Correct positioning required fluoroscopic guidance and considerable technical skill.

To overcome these difficulties, Lategola and Rahn, in 1953, constructed a self-guiding catheter (3).

The catheter was approximately 3 feet long, 10 French wide, and consisted of two tubes. The outer tube was used for pressure measurement and blood withdrawal, while the inner tube served to inflate a rubber balloon. After insertion into the jugular vein, the larger tube was connected to a saline manometer and the balloon was partially inflated. In the author's words, "The balloon acted as a sail and swept the catheter through the right heart and into the pulmonary artery." The entire procedure was rapid and, after insertion of the catheter into the jugular vein, required no particular skills, since even medical students were able to perform it. The only disadvantage consisted of the frequent development of clots along the folds of the balloon. Unfortunately for the authors, and humankind, the technique remained limited to the dog lab, and the catheter was never used in humans.

Swan-Ganz Catheter. Several other self-guiding catheters were subsequently described, but none achieved great acceptance until 1970, when Swan, Ganz, and their colleagues published their results with a new catheter (4).

The flow-directed, balloon-tipped catheter was a double lumen polyvinyl device with a small latex balloon located one millimeter from the catheter tip. It was advanced under pressure and electrocardiographic control. In the first 100 attempts, the average time for passage of the catheter from the right atrium to the pulmonary artery was 35 seconds. Failure to enter the pulmonary artery occurred in 8% of passages, and 13% of patients developed premature ventricular contractions. The integrity of the balloon was disturbed in 10 cases, but no symptoms or complications could be attributed to this fact. In 2 patients, one of whom died of pulmonary embolism, thrombosis was observed around the shaft of the catheter. The major advantage of the new catheter was that the pulmonary artery could be catheterized at the bedside without fluoroscopy.

Shortly after its introduction, the Swan-Ganz catheter was further improved by the addition of a thermistor for cardiac output determinations (5). One injects 10cc of iced 5% dextrose in water into the right atrium; the thermistor at the tip of

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the catheter measures the temperature change in the pulmonary artery. After a short delay, the temperature in the pulmonary artery declines, reaching a maximum deviation from baseline in about six seconds; the return to baseline occurs in an exponential manner. A small computer integrates the values of the changing blood temperature over time, and calculates cardiac output. Close correlation between thermodilution and dye-dilution has been demonstrated over a wide range of outputs, both in experimental animals and in humans (6).

The major advantage of the thermodilution technique is that measurements can be repeated rapidly. Serial cardiac outputs provide a better understanding of a patient's cardiovascular status, and allow one to study the response of different therapeutic maneuvers.

Anesthesiologists quickly realized the potential of the new technique, and as early as 1972, reports began to appear about the use of pulmonary artery catheters during anesthesia. Civetta and Gabel observed that, in surgical patients, the correlation between the central venous pressure and the pulmonary capillary wedge pressure was often unpredictable (7).

At approximately the same time, Lapas showed that an excellent correlation existed between the left atrial pressure and the pulmonary wedge pressure, while the correlation between the left atrial pressure and the pulmonary artery diastolic pressure was almost as good (8). It thus became evident that central venous pressure and pulmonary capillary wedge pressure were not interchangeable.

A tool to assess left ventricular function was now readily available, and over the years, anesthesiologists made avid use of it.

Present

Today, the fairly simple device introduced a decade ago has become quite sophisticated, and many different models are now available. The new features include pacing wires, optic fibers, and additional infusion ports. To prevent thrombosis, the catheters are now routinely coated with heparin.

Improvements in design, however, have not prevented all complications. Although some of the accidents are related to central venous cannulation, others are directly due to the presence of the catheter in the pulmonary circulation. Rupture of the pulmonary artery is the most damaging accident, producing high morbidity and mortality (9). As with many invasive procedures, the major cause of complications is an operator's lack of experience (10). In experienced hands, the incidence of complications is low and the potential benefits great.

Indications for insertion of the catheter vary widely according to differing views among anesthesiologists, but monitoring of left ventricular performance is usually the goal. The determinants of cardiac output, and thus ventricular performance, are the heart rate, rhythm, preload, afterload, and contractility. From the pulmonary artery catheter we obtain the cardiac output and the preload. We can combine this information with the arterial pressure and calculate the vascular resistance and stroke-work indices. We then assume that the pulmonary capillary wedge pressure adequately reflects the left ventricular volume and that the cardiac output, or stroke work, represents the mechanical work of the heart. Those two variables are placed on the axes of a Frank Starling diagram. The contractility is represented by a curve which moves upward when the contractility increases and downward when the contractility decreases (11). It has been suggested that for each patient, a plot should be constructed, and that changes in the patient's condition should be followed on the diagram. The patient's response to different therapeutic maneuvers can then be identified and the most appropriate management initiated (12).

Frank Starling Diagram. Not all hemodynamic interventions, however, can be fitted easily into the Frank Starling diagram. We would all agree that halothane is a potent myocardial depressant, and it is therefore normal that increasing doses of halothane produce a downward shift of the cardiac contractility curve (13). But it is not always that simple.

Opposite findings were obtained by Roizen and Hamilton, who studied 44 patients undergoing major aortic surgery under halothane or ethrane anesthesia (14). During surgical stimulation, they observed 15 episodes of marked elevation in pulmonary capillary wedge pressure, without change in cardiac output. When those abnormalities were noted, the only therapy consisted of a 50% increase in the concentration of the volatile agents, and in all patients this produced a return to normal values. On a Frank Starling diagram, the surgical stimulation of these anesthetized patients produced a shift to a depressed curve. An increase in the halothane concentration did not result in further myocardial depression but produced a better performance curve.

How do we explain these disturbing findings? Halothane affects both myocardial contractility and the peripheral vascular resistance. Cardiac performance is diminished by halothane's myocardial-depressant effect but is improved by its afterload-reducing effect. The ventricular-function curve reflects those combined influences, but does not allow us to differentiate between them. A similar phenomenon is observed when one looks at the actions of various drugs on ventricular function in patients with congestive heart failure. Phentolamine, sodium nitroprusside, and digitalis improve the function of the failing heart by producing an almost similar shift to a better function curve (15). Digitalis, however, does this by improving contractility, while the two others have no influence at all on contractility but produce vasodilatation.

The information provided by the pulmonary artery catheter thus allows us to assess ventricular function, but does not allow us to differentiate the influence of changes in contractility from changes in loading conditions.

Contractility. Is it possible to measure changes in contractility independently of variations in afterload? Assessing contractility is clearly difficult; witness the many indices suggested over the years. Traditional indices are obtained either during the isovolumetric phase of the contraction or during the ejection phase. The isovolumetric-phase indices are, as a rule, particularly sensitive to changes in preload. The ejection-phase indices, on the other hand, are afterload sensitive. One useful improvement in the Swan-Ganz catheter would be a feature which allows the measurement of contractility directly and independently of preload and afterload.

Additional Findings. Recently, a new indication for the use of the Swan-Ganz catheter has been suggested. Kaplan and Wells have studied patients undergoing coronary artery bypass grafting and have established that elevation of the pulmonary capillary wedge pressure and changes in the pulmonary capillary wedge tracings are early indicators of myocardial ischemia (16). They diagnosed ischemia in 45% of their patients. They then divided their ischemic patients into 3 groups. The patients in Group 1 had electrocardiographic signs of ischemia, without changes in wedge tracing. Patients in Group 2 had electrocardiographic signs of ischemia, plus changes in pulmonary capillary wedge tracing. In Group 3, the only sign of ischemia was an abnormal pulmonary capillary wedge tracing. They further observed that in the two groups with elevated pulmonary artery pressures, the central venous pressure was also significantly increased. The authors then concluded that changes in left ventricular compliance were the first signs of ischemia, and that certain rises in pulmonary capillary wedge pressure would be indicative of these changes in compliance.

Lieberman and colleagues, studying predictors of ischemia in 30 coronary artery bypass patients, confirmed these findings. They also demonstrated significant increases in pulmonary capillary wedge pressure in the presence of ischemia (17). They divided their patients into three groups. Patients in Group I had normal left ventricular function; patients in Group II had moderately impaired left ventricular function; patients in Group III had severely depressed left ventricular function. Only one patient in Group III had ischemic episodes with increased pulmonary capillary wedge pressure, without simultaneous increases in central venous pressure. On the other hand, 20 episodes were noted in which central venous pressure was the only predictor of ischemia, while the wedge pressure remained unchanged.

If the detection of ischemia becomes a new indication for the use of invasive monitoring, it would be important to determine which ventricle should be monitored for the earliest possible diagnosis. We should then further establish if the pulmonary artery catheter has a role to play in this monitoring, and what modifications, if any, would improve its use.

Future

Now, I would like to develop the following points: First, I shall try to demonstrate that precise definition of the left ventricular function and detection of left ventricular ischemia requires knowledge of right ventricular performance. Second, I would like to show that ventricular function can only be determined accurately if ventricular volume is known. Finally, I shall introduce a new type of pulmonary artery catheter which measures right ventricular volumes.

Left Ventricular Function and Right Ventricular Performance. Placing left ventricular volumes on the horizontal axis and left ventricular end-diastolic pressures on the vertical axis of an X–Y diagram yields a compliance curve. Normally, large changes in end-diastolic volume produce small changes in end-diastolic pressure (18). At low left ventricular end-diastolic pressure, this results in a linear relation with a gentle upward slope. At the upper limits of normal left ventricular end-diastolic pressure, the curve becomes steeper and approximates an exponential relation.

During ischemia, a reduction in compliance has been demonstrated by numerous authors (18, 19). The reduction in compliance results in a leftward and upward shift to a totally different pressure-volume curve. Thus, at equal pressure, the ischemic ventricle contains a smaller blood volume. Other acute interventions, such as the administration of angiotensin, can similarly produce an upward shift of the compliance curve (20).

To understand the displacement of the compliance curve, we have to analyze the factors which determine the diastolic pressure-volume relationship of the left ventricle. The factors can be divided into three categories. They are related to either the mechanical properties of passive cardiac muscle, the external forces surrounding the ventricle, or the left ventricular geometry.

Numerous studies have emphasized early relaxation abnormalities in ischemic heart disease. The impaired ventricular relaxation, however, is insufficient to account for the marked shifts in compliance observed during angina (21). For that reason, in recent years, particular attention has been focused on the external forces acting on the left ventricle, specifically, the pericardium and the right ventricle (22). The importance of the pericardium was clearly illustrated in the studies of Shirato on conscious dogs (23). Acute overtransfusion with dextran shifts the diastolic pressure-volume curve upwards, while nitroprusside lowers the curve towards normal. If the dog's pericardium has been removed, however, all pressure-volume points fall along a single curve.

The second external force acting on the left ventricle is the right ventricle. The importance of right ventricular distention on left ventricular compliance was clearly demonstrated by Sibbald, who studied three groups of patients with adult respiratory distress syndrome (24). The first group had no pulmonary artery hypertension; the second group had moderate pulmonary artery hypertension; the third group had severely elevated pulmonary artery pressures. For equal left ventricular end-diastolic volumes, there were marked differences in left ventricular filling pressures. Volume infusion, in an attempt to increase preload, produced a much larger increase in wedge pressure in group 3 than in group 1.

Further evidence that sudden right ventricular distention can decrease left ventricular compliance was provided by the observations of Brinker, who produced sudden right-ventricular loading by asking his subjects to perform a forced inspiration against a closed airway (25). Septal shape and right and left ventricular size were evaluated by echocardiography.

Acute right ventricular loading altered the configuration of the interventricular septum in both the systolic and diastolic phase. The leftward displacement and flattening of the septum produced a considerable decrease in left ventricular size. The entire heart should be envisioned as a two-layer shell in which a relatively elastic layer of ventricular wall is applied to the interior of a much stiffer outer shell, the pericardium. The elastic septum divides this composite shell into two ventricles. If a sudden increase in left ventricular afterload occurs, it produces an increase in left ventricular end-diastolic pressure. This in turn raises right ventricular afterload, leading to right ventricular distention and displacement of the septum, which then produces a further decrease in left ventricular compliance (Fig. 1).

The increase in left ventricular afterload and in left ventricular end-diastolic pressure can both lead to ischemia. A crucial element in this vicious cycle is the right ventricle's ability to handle the increased afterload. If right ventricular function is depressed, distention will occur and left ventricular compliance will decrease.

Vasodilators produce peripheral and pulmonary vasodilatation and thus reduce left and right ventricular afterload. Their most important effect, however, might be to produce venous pooling which, in turn, decreases right ventricular distention.

Factors in Right Ventricular Function. Having demonstrated the importance of right ventricular function, let us now analyze the factors which determine it. They are similar to those determining left ventricular function, with the difference that the right ventricle is more sensitive to afterload and has a limited ability to increase contractility. Right ventricular afterload can be estimated from the mean pulmonary artery pressure, but, as for the left side, contractility is difficult to measure.

In 1974, Suga and Sagawa, who were studying left ventricular pressure-volume loops in dogs, realized that for a given level of contractility, all the end systolic pressure-volume points were positioned on a straight line (26). They further demonstrated that this linear relationship was particularly sensitive to inotropic interventions. These same findings were later confirmed in humans (27).

In 1979, Maughan demonstrated that this linear relationship could also be established for

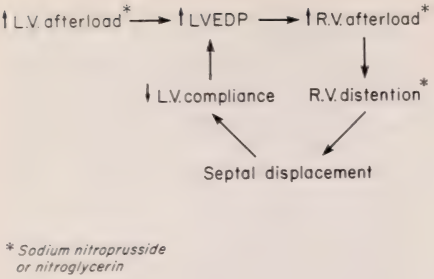
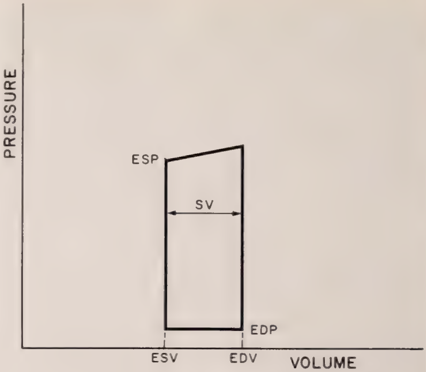

↑ L.V. afterload*
↑ LVEDP
↑ R.V. afterload*
↓ L.V. compliance
R.V. distention*
Septal displacement
* Sodium nitroprusside or nitroglycerin

Fig. 1.

the right ventricle (28). The importance of these findings lies in the fact that this index of contractility is independent of preload and afterload.

Pressure-Volume Analysis and Ventricular Volume. Since these observations are so meaningful, the concepts of pressure-volume analysis (Fig. 2) should become familiar. The ventricular volume is on the abscissa, while the pressure is placed on the ordinate. The EDP point represents the preload, or left ventricular volume, and pressure at the end of diastole. The upward limb describes the isovolumetric contraction resulting in a pressure increase without change in volume, leading to the opening of the aortic valve and ejection. At the end-systolic point, the ventricle terminates its contraction and the relaxation phase begins. Stroke volume is, by definition, the difference between the end-diastolic volume and the end-systolic volume.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VOLUME

Fig. 2.

For a given contractile state, all end-systolic pressure points will fall on the same line (Fig. 3). If preload remains constant, the stroke volume is inversely proportional to the end-systolic pressure. Thus, the greater the end systolic pressure, the smaller the stroke volume. Positive inotropic intervention will result in a leftward shift of the end-systolic pressure volume slope, while myocardial depression produces a rightward displacement of the slope (Fig. 4).

Analysis of this graph then reveals that for a given preload and constant end-systolic pressure, the stroke volume increases with an increase in contractility. That the measurement of contractility by pressure volume analysis can provide

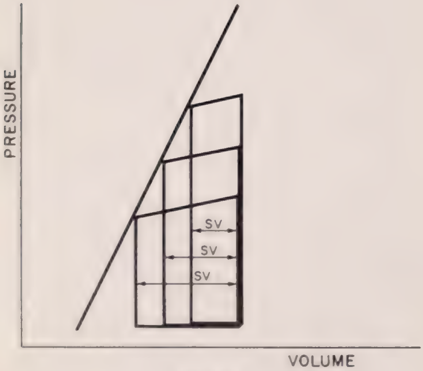
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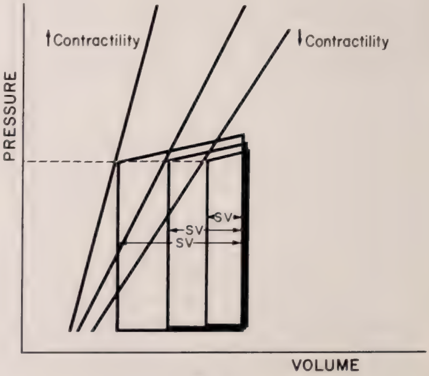
Fig. 3.


↑ Contractility
↓ Contractility
PRESSURE
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VOLUME

Fig. 4.

useful information was elegantly demonstrated by Sibbald (24) in his study of patients with adult respiratory distress. He described three groups: no pulmonary artery hypertension, moderate hypertension, and severe hypertension. When the right ventricular function of these patients was represented on a standard Starling diagram, specifically with the preload on the horizontal axis and the mechanical work on the vertical axis, the three groups fell on a similar ventricular-function curve. When this information is then transferred to a pressure-volume diagram, it becomes evident that those patients with severe pulmonary hypertension also suffer from severe right ventricular dysfunction. Only by pressure-volume analysis could this depression be detected.

If we try to construct pressure-volume loops from our usually available hemodynamic information, we find that for the left ventricle, the pulmonary artery catheter provides us with the end-diastolic pressure, or wedge pressure, and the stroke volume. The left ventricular end-systolic pressure can be measured at the dicrotic notch of a systemic arterial pressure tracing. For the right ventricle we can use the central venous pressure, the stroke volume, and the pulmonary artery pressure. The missing elements, however, are either the end-diastolic volume, the end-systolic volume, or the ejection fraction.

A New Catheter. Many methods for volume measurements have been described, but most are too cumbersome for use in the operating room. One method is based on dye-dilution and therefore deserves our attention.

It has been known since 1951 that right ventricular volume can be measured by injection of Evan's blue (29). Attempts to substitute iced saline solution for Evan's blue had thus far been frustrated by inadequate technology. The response time of the standard pulmonary artery thermistor, currently around 1000 milliseconds, was too slow to obtain adequate volume calculations. In 1983 Kay and colleagues described their results with a new pulmonary artery catheter on which a fast-response thermistor is mounted (30). This catheter differs from standard Swan-Ganz catheters by the addition of right ventricular injection ports and the presence of intracardiac electrocardiograph electrodes. Using the fast-response thermistor, individual beats can be identified on a thermal response curve. From this information, the residual fraction and ejection fraction can be computed. End-diastolic and end-systolic volumes can then be calculated from the cardiac output and the ejection fraction.

The knowledge of right ventricular volume enables us to define right ventricular function precisely, and it is not inconceivable that this knowledge will markedly contribute to the early diagnosis of left ventricular ischemia.

It is somewhat ironic that, whereas ten years ago the pulmonary artery catheter was introduced as a tool to evaluate left ventricular function, it may in the future become the instrument of choice for assessment of right ventricular performance.

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Evoked Potentials in the Operating Room

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Sensory evoked potentials are the electrophysiologic responses of the nervous system to sensory stimulation (1, 2). They are used to assess the functional integrity of sensory pathways in anesthetized or comatose patients when clinical or neurological assessment is severely limited (3, 4). The activity elicited by sensory stimulation is extracted from the background electroencephalographic activity by summation or averaging, and the resulting evoked potential waveforms are displayed as plots of voltage against time after sensory stimulation. Characteristic peaks can be reproducibly identified and measured in terms of poststimulus latency and amplitude.

Although the structures from which these peaks arise have not been definitely identified, specific neural generators have been postulated on the basis of studies done in animals and clinical pathological correlations in humans.

Visual and auditory evoked potentials are used to assess sensory function in infants, in patients who are suspected of hysteria or malingering, and in patients who are mentally handicapped or otherwise unable to cooperate with traditional sensory testing. Nerve conduction studies are used to assess peripheral neuropathy.

The most widespread use of evoked potential recording in diagnostic neurology has been in the diagnosis of multiple sclerosis, when evoked potentials are often abnormal even before clinical signs of dysfunction in an affected pathway become apparent. Evoked potential studies for the purpose of detecting mass lesions or ischemic areas in the central nervous system are becoming less important with the increasing sophistication of neuroradiologic diagnostic capabilities such as computerized tomography, positron emission tomography, and magnetic resonance imaging.

The most important applications of evoked potential testing in the future may well be for monitoring of specific neural pathways in the operating room and critical care unit, where repeated measurements can be made using portable equipment and noninvasive techniques.

Indications for Intraoperative Monitoring

Intraoperative monitoring of sensory evoked potentials may be valuable when four conditions are satisfied: (a) neural pathways at risk are amenable to monitoring; (b) personnel and equipment are available for recording and interpreting evoked potentials; (c) appropriate sites are available for stimulation and recording during the contemplated operative procedure; and (d) some possibility exists that, if impulse transmission deteriorates intraoperatively, interventions can be made to improve neurologic function acutely and minimize the possibility of permanent neurologic injury.

Visual evoked potentials are monitored during operations on the pituitary gland and during neurosurgical operations in the anterior cranial fossa (3–6).

Brainstem auditory evoked potentials are monitored during operations in the posterior cranial fossa, when the eighth cranial nerve and the brainstem may be subject to injury (7).

Somatosensory evoked potentials are monitored during operations on the spine, particularly when the spine is unstable or when some degree of myelopathy has been detected preoperatively (8–11). Spinal cord function is known to be at risk

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during the operative treatment of scoliosis (12), particularly when Harrington rod instrumentation or posterior wiring is employed. During neurosurgical operations, cord function may be affected by surgical retraction, deliberate or accidental hypotension, operative manipulation, or movement of an unstable spine (9). Most of these changes are reversible if they are detected promptly. Cortical somatosensory evoked potentials can detect cerebral ischemia secondary to hypotension, artery-to-artery embolism, temporary occlusion of a carotid artery for carotid endarterectomy (13), or complications associated with cardiopulmonary bypass (14).

Classifications of Evoked Potentials

Evoked potentials may be classified according to the mode of stimulation, the poststimulus latency of peaks or complexes in the waveform, the distances separating purported neural generators from recording electrodes, and the structures in which the potentials are thought to arise.

The modes of sensory stimulation used for intraoperative evoked potential monitoring are somatosensory, auditory, and visual. The somatosensory stimulus consists of a brief electrical shock given to a sensory or mixed peripheral nerve. Visual stimulation consists of flashes delivered by light-emitting diodes mounted in opaque goggles over closed eyelids. For auditory stimulation, either clicks or tones can be delivered through ear-insert transducers.

The poststimulus latency of a peak or complex in an evoked potential waveform is the time in milliseconds after the sensory stimulus at which that peak or complex occurs. Poststimulus latencies may be short (less than 10 milliseconds to approximately 40 milliseconds), intermediate (approximately 20 to 120 milliseconds) or long (approximately 100 to 500 milliseconds). The short-latency potentials, arising nearest the site of stimulation, are minimally affected by pharmacologic and physiologic manipulations. Intermediate-latency potentials arise in the primary sensory area of the cerebral cortex. They are affected by anesthetic agents but are definitely useful for intraoperative monitoring. The evoked potentials of long poststimulus latency are so sensitive to drugs and to subtle physiologic alterations that they have not been made useful for intraoperative monitoring.

The distances separating purported neural generators from recording electrodes serve to classify evoked potentials as either "near-field" or "far-field." Near-field potentials when recorded from the scalp arise in the cerebral cortex, usually within approximately 2 centimeters of the recording electrode. Far-field potentials are transmitted to the electrode by volume conduction from generators that may be inches or feet away. Signal strength falls as the distance from the source increases, so that voltages of far-field evoked potentials are smaller than those of near-field potentials, and larger numbers of repetitions must be averaged to make these waveforms apparent.

The purported generators of sensory evoked potentials include the sensory receptors themselves, peripheral or cranial nerves, nerve plexuses, the spinal cord, and both subcortical and cortical structures in the brain. No definite proof of the specific neural generators of particular peaks in evoked potential waveforms has been found, but evidence from studies done in animals and from clinical pathological correlations in humans supports several clinically useful designations.

Methods

Although other methods of signal processing have been described, most clinical evoked potential recording depends on averaging or summation of multiple responses to repetitive sensory stimulation. Epochs of neurophysiologic activity are recorded immediately following each sensory stimulus. Since the background spontaneous electroencephalogram is to some extent random, the ratio of the evoked potential signal to the background electroencephalographic noise increases according to the square root of the number of repetitions.

Equipment. A number of manufacturers provide "turn-key" evoked potential recording systems with packaged hardware and software more or less ready to use. Alternatively, hardware components can be purchased and assembled locally. The development of software (programs for the computer) is time-consuming and frustrating, however. Most manufacturers currently estimate that the cost of software development exceeds the cost of hardware by ten times or more.

Regardless of its source, a complete system for monitoring evoked potentials provides for acquisition and conditioning of electrophysiologic signals; signal processing, including summation or averaging; display and measurement of evoked potential waveforms; and data storage. A number of options to facilitate monitoring in the operating room are also available.

Signal conditioning is accomplished using filters and amplifiers to exclude signals outside the frequency bands of interest and to magnify the small voltages of the recorded electrophysiologic activity. Summation or averaging, as well as time-locking of sensory stimulation and data acquisition, is accomplished using a microprocessor or small computer. Averaged evoked potential waveforms are displayed on an oscilloscope for precise measurement with electronic cursors, then plotted to provide a permanent record. Electromagnetic data storage on disk or tape may be provided as well.

Options are available for automatically rejecting data segments contaminated with high-amplitude artifact, but with currently available systems, artifact of lower amplitude can only be eliminated by constant monitoring of the unprocessed signal and manual suspension of the averaging process when the signal appears to be noisy.

Like any other equipment used in the operating room, evoked potential monitoring systems must meet electrical safety standards. Leakage from the system to the patient should be less than 10 microamperes and from the system to the case less than 100 microamperes. All devices connected to a patient in the operating room should be linked by a common isolation grounding bus. Components should be securely mounted to a rack that can be safely moved without tipping, and provision should be made to prevent overheating of equipment or damage from blood and other fluids.

Sensory Stimulation. Methods of sensory stimulation used in the operating room of necessity differ somewhat from the methods used in the diagnostic electrophysiologic laboratory. Special consideration must be given to patient safety and to avoidance of the sterile surgical field.

Somatosensory stimulation is best provided using subdermal platinum electrodes. Electrical currents of 2 to 20 milliamperes are delivered by electrode pairs placed along a nerve trunk approximately 3 centimeters apart, with the cathode proximal. The stimulus is usually 200 to 300 microseconds in duration, and hundreds of patients have been monitored repetitively for many hours with no apparent harm.

Surface electrodes are commonly used for somatosensory stimulation in the diagnostic laboratory; but some degree of pressure is necessary to achieve adequate stimulation with low currents, and sustained pressure on the skin during anesthesia might cause ischemic damage. Furthermore, surface electrodes can be displaced under the surgical drapes and, when neuromuscular blocking agents are given to provide muscle relaxation, one cannot see the visible motor twitch that confirms adequate stimulation of a mixed nerve. The higher impedance of needle electrodes compared to surface electrodes is not a problem for sensory stimulation because the duty cycle of the stimulating electrodes is very short. Furthermore, the constant-current stimulators most frequency employed automatically compensate for small changes in electrode impedance related to polarization during a procedure.

Auditory stimulation is best accomplished using ear-insert transducers with rigid or semirigid ear pieces. Pliable ear pieces can be compressed intraoperatively, obstructing the transmission of acoustic stimuli to the tympanic membrane and causing a loss of the evoked potential secondary to the loss of sensory stimulation. The large stimulus artifact which results from the proximity of the transducer to the earlobe electrode can be satisfactorily attenuated by using clicks of alternating polarity.

Visual stimulators that are currently available are not fully satisfactory. Several manufacturers supply arrays of light-emitting diodes mounted in opaque goggles. These can be used over closed eyelids to provide a diffuse flash stimulus, but the goggle housing often encroaches upon the surgical field during operations in the anterior cranial fossa. Should the stimulator be pushed off the bony ridge of the orbit during such an operation and put direct pressure on the globe of the eye, central retinal artery thrombosis could be produced with completely untreatable permanent blindness. Some investigators have used light-emitting diodes mounted in contact lenses for intraoperative visual stimulation. This seems quite reasonable during major craniofacial procedures when large scleral lenses are used to protect the globe of the eye intraoperatively. Many anesthesiologists, however, would feel some degree of concern about placing a foreign object in the eye when it might be subject to pressure but could not be directly observed for many hours. Better visual stimulators are needed.

Recording. Cup or disk electrodes, placed at specific measured locations according to the International Ten Twenty System, are attached to the scalp with collodion, filled with salt gel, and sealed with plastic tape to prevent drying. Electrode wires are taped to the skin to provide strain relief, then twisted together and secured away from sources of electrical or mechanical disturbance. Silver/silver chloride electrodes are best, but gold or tin electrodes may also be used. Interelectrode impedances should be 3,000 ohms or less. Electrodes applied using this technique can remain electrically and mechanically stable for 24 hours or longer.

Anesthetic Management

Whether or not anesthesiologists assume a primary role in recording and interpreting evoked potentials, the anesthesiologist has important responsibilities in facilitating this electrophysiologic monitoring. A multiplicity of factors under the control of the anesthesiologist can alter evoked potentials, and difficulties may arise in distinguishing those evoked potential alterations related to anesthetic manipulations from changes due to operative maneuvers carried out by the surgeon. The evoked potential changes produced by anesthetics are, and should always be, reversible and should not prompt alteration of the contemplated surgical procedure. In contrast, a loss of evoked potential activity related to operative manipulation may well indicate a need for modification of the procedure that is underway. For example, the degree of distraction on Harrington rods might be lessened or the rods might be removed. An alternative approach to a tumor might be attempted. In some cases, evoked potential alterations might prompt a decision to abandon a risky neurosurgical procedure. Should any of these steps be erroneously taken when evoked potential changes were actually due to reversible effects of anesthetic agents, the patient might suffer needlessly.

The anesthesiologist can minimize this kind of confusion by maintaining the patient in a relatively constant physiologic and pharmacologic state, particularly during critical operative maneuvers.

Halogenated anesthetics should be avoided when potentials of cortical origin are to be monitored.

Bolus injections of agents that can affect evoked potentials should be avoided during critical phases of the operation, and monitoring is often facilitated by giving intravenous drugs in a slow constant infusion, rather than by intermittent bolus injection.

The anesthesiologist should also monitor and constrain, in so far as possible, the multiple variables, such as body temperature, tensions of arterial blood gases, and arterial blood pressure, that are known to affect evoked potentials.

When only potentials of subcortical origins are to be monitored, virtually any anesthetic technique can be used. Maintenance of a relatively steady state is still helpful, however, and temperature changes can have marked effects on the short-latency subcortical potentials as well as on cortical potentials.

Analysis of Clinical Experience

Evoked potential monitoring techniques can be assessed in terms of feasibility, cost, sensitivity, utility, and reliability. To assess feasibility, we can look at the incidence of technical difficulties that force abandonment of monitoring. The cost of monitoring can be examined in terms of requirements for operating-room time, personnel, equipment, and supplies. The events associated with intraoperative changes in evoked potentials provide an index of the sensitivity of these techniques, and utility can be assessed by enumerating the interventions that are made on the basis of monitoring data. Reliability can be estimated by examining the correlations between intraoperative evoked potential findings and neurologic outcomes.

Somatosensory Potentials. The most extensive experience with intraoperative evoked potentials to date has been with somatosensory evoked potentials.

Since the 1975 report of the Scoliosis Research Society on neurologic injuries associated with operative treatment of scoliosis (12), increasing numbers of orthopedic surgeons monitor spinal cord function intraoperatively, either by awakening patients to test voluntary motor function or by monitoring somatosensory evoked potentials. Intraoperative alterations in somatosensory evoked potentials are seen more frequently during high-risk neurosurgical procedures, however, than during orthopedic operations. Changes have been associated with operative manipulation (15), hypotension (16), surgical retraction (9), and systemic hypoxia (17).

Somatosensory evoked potentials can guide surgical treatment of the traumatized brachial plexus and deliberate lesioning of the dorsal roots of signal nerves or the dorsal root entry zones of the cord. Somatosensory evoked potentials recorded from the cerebral cortex can localize the sensorimotor strip for the neurosurgeon, so that this area and its vascular supply can be preserved during the resection of adjacent lesions. Somatosensory central conduction times are useful for detecting cerebral ischemia during temporary carotid occlusion during carotid endarterectomy, indicating the need for an intraluminal shunt, and for determining appropriate levels of induced hypotension for operations on intracranial aneurysms (13).

The same recording montage as that used to record Fig. 1 can also be used to record potentials elicited by any one of the four extremities. Comparison of potentials at risk from operative manipulation to potentials not at risk from surgical maneuvers helps to distinguish those changes originating at the operative site from changes due to anesthesia or other systemic factors. As a general rule, recording in multiple channels greatly aids the interpretation of evoked potentials.

Somatosensory evoked potentials are the most technically difficult to record of those evoked potentials commonly monitored in the operating room. Some observers have obtained a number of technically inadequate studies. The correlation between intraoperative somatosensory evoked potential findings and postoperative neurologic function has generally been good, but some exceptions have been reported. Erroneous results may have been related to problems with quality control in an electrically hostile recording environment or to alterations in evoked potentials produced by anesthetics or other extraneous factors.

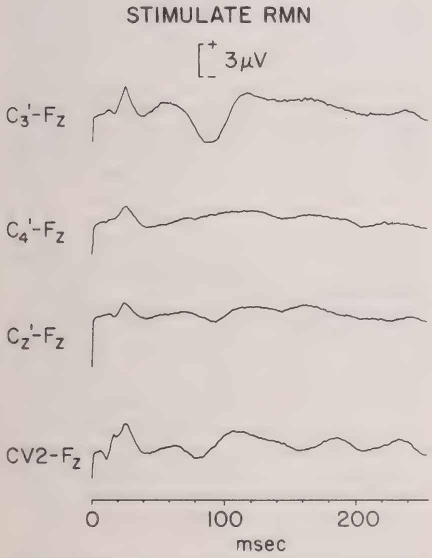


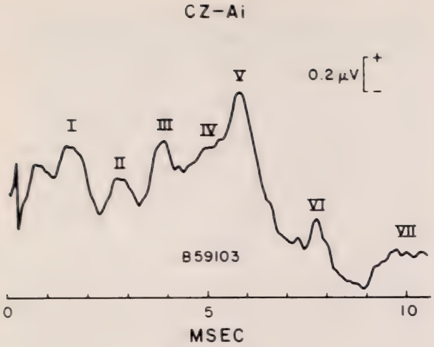
Fig. 1. Normal somatosensory evoked potentials recorded simultaneously from scalp and neck. Both cortical and subcortical peaks are apparent, and the same recording montage is used during stimulation of any one of the four extremities. Reprinted with permission from Grundy BL (4).

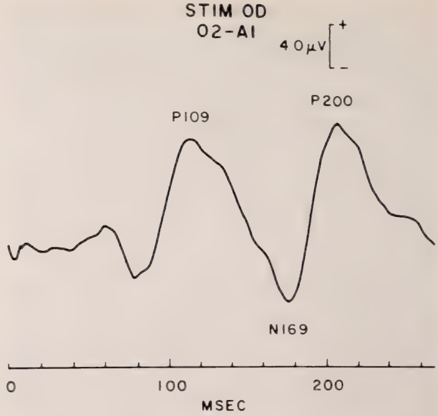
Brainstem Auditory Potentials. Fig. 2 shows a normal brainstem auditory evoked potential waveform. These short-latency far-field potentials are entirely subcortical in origin. They may be abnormal preoperatively in patients scheduled for posterior fossa craniotomy, but even abnormal waveforms are valuable for intraoperative monitoring if they are reproducible.

Abnormalities of brainstem auditory evoked potentials may relate to either audiologic or neurologic problems. Ideally, audiograms should be obtained preoperatively for all patients who are to have brainstem auditory evoked potentials monitored in the operating room. At the very least, threshold hearing levels to the stimuli that will be used intraoperatively should be determined before the induction of anesthesia whenever possible. If brainstem auditory evoked potentials are absent in comatose patients or infants, the electrocochleogram should be recorded from an electrode placed in the external auditory meatus to rule out a peripheral audiologic abnormality as the cause of the absent brainstem auditory evoked potential.

We saw changes thought to be clinically important during 37 of our first 54 cases monitored with brainstem auditory evoked potentials during operations in the posterior cranial fossa (7). Operative retraction was the most frequently associated factor. Changes were also seen with the positioning of the head for retromastoid craniectomy, with operative manipulation, and with the combination of relative hypotension and hypocarbia. Five patients irretrievably lost brainstem auditory evoked potentials intraoperatively. Each had diminished hearing and markedly abnormal potentials preoperatively, and in each of these 5 the eighth nerve had to be deliberately sacrificed during the course of the surgical procedure. All of these patients were completely deaf on the affected side after operation. In the other 32 cases, the changes in brainstem auditory evoked potentials were reversible in the operating room and hearing was preserved in each of these.

Visual Potentials. Although ophthalmologists have gained considerable experience with the electroretinogram, little is known about subcortical visual evoked potentials. Only cortical flash-evoked potentials have been monitored during anesthesia and operation. A normal flash-evoked potential is shown in Fig. 3.





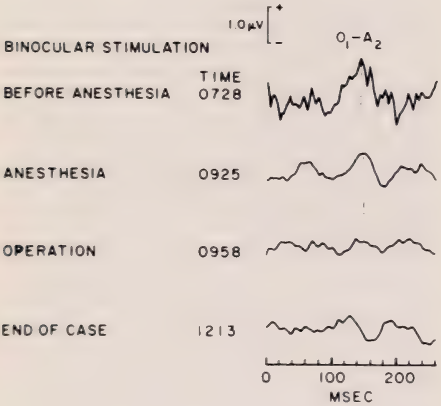


Fig. 2. Top left Normal brain stem auditory evoked potential, recorded from vertex (CZ) to earlobe ipsilateral to auditory stimulation (Ai). Purported generators of labeled peaks are: I, extracranial portion of auditory nerve; II, intracranial portion of auditory nerve and/or cochlear nucleus; III, superior olive; IV, lateral lemniscus; V, inferior colliculus; VI, medial geniculate; and VII, thalamocortical radiations. Reprinted with permission from Grundy BL (3).

Fig. 3. Top right Normal visual-evoked potential elicited by flash stimulation over closed eyelids. Nominal P100, here 109 ms after stimulation, arises in occipital cortex and is the most important marker for intraoperative monitoring. Reprinted with permission from Grundy BL (3).

Fig. 4. Bottom left Visual-evoked potentials recorded during transphenoidal resection of pituitary tumor. Transient deterioration of VEP was followed by recovery, with shorter poststimulus latency of nominal P100 than seen prior to resection of tumor. Patient's visual function was improved after operation. Reprinted with permission from Grundy BL (3).

Visual evoked potentials are most useful during operations on the pituitary gland and during neurosurgical operations in the anterior cranial fossa. Several investigators have become disillusioned with this technique, perhaps because of the technical difficulties involved, the inadequacies of the available visual stimulators, and the exquisite sensitivity of visual evoked potentials to general anesthetics. Nevertheless, a number of investigators continue to find this monitoring modality useful. Figure 4 shows improvement in visual evoked potentials which were abnormal preoperatively because of a large recurrent pituitary tumor associated with visual field defects. The flash-evoked potential was more nearly normal after the resection of the tumor, and vision was improved postoperatively as documented by formal visual field testing.

New techniques and protocols are needed to make intraoperative monitoring of visual evoked potentials more reliable.

Current Limitations. The evoked potential monitoring of today resembles in some respects the electrocardiographic monitoring of several decades ago. The techniques are cumbersome and somewhat expensive. Meticulous attention to the details of signal acquisition and processing is required. The numerous variables that can confuse intraoperative interpretation of evoked potentials are not yet adequately defined and quantitatively characterized. Personnel qualified to record and interpret these waveforms in the operating room are scarce. The available clinical data base is small; and the parameters of greatest interest, with their appropriate quantitative tolerance limits, have not yet been fully defined. Much still depends on the Gestalt pattern recognition skills of an experienced observer, and this is a hindrance to more rapid diffusion of this technology

Conclusions

Despite the current limitations of available technology, intraoperative monitoring of evoked potentials is clearly feasible. With careful attention to quality control, reproducible recordings can be obtained that are sensitive to events of interest in the operating room. The information provided can be used to prompt interventions that optimize neurologic function intraoperatively, and several reports strongly suggest that at least some instances of permanent neurological injury may be averted. Because of the devasting nature of such injuries, considerable effort seems justified if neural function can be preserved.

Yet we still lack adequate information on the incidence of neurologic complications, and we do not yet know with what reliability intraoperative monitoring may help to prevent them. As evidence accumulates, however, and as equipment and techniques become simpler to use and perhaps less expensive, intraoperative monitoring of evoked potentials can be expected to find increasing widespread application. Within a decade, these methods will probably be used in most large medical centers, and in many community hospitals as well, for patients undergoing high-risk neurosurgical, vascular, orthopedic, and cardiac operations.

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Transesophageal Echocardiography

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The hemodynamic and left ventricular functional changes that occur during both cardiac and noncardiac surgery reflect a variety of influences. Standard monitoring of blood pressure, heart rate, and the electrocardiogram do not allow the anesthesiologist to be fully informed of these changes. In recent years, pulmonary artery catheterization has permitted use of the Frank-Starling relationship intraoperatively to assess left ventricular function. The vertical axis is usually represented by the cardiac output or blood pressure; the horizontal axis of left ventricular preload is represented by the pulmonary capillary wedge pressure (PCWP). However, the PCWP provides a good representation of the true preload, left ventricular end-diastolic volume (LVEDV), only if airway pressure and mitral valve function are normal, and myocardial compliance is normal and unchanging. This last assumption is often incorrect, since patients with coronary artery disease or valvular heart disease have abnormal left ventricular compliance, and episodes of intraoperative ischemia often lead to further decreases in compliance. In addition, this monitoring does not allow for a true measure of myocardial contractility. Echocardiography holds the promise of on-line measurements of LVEDV and myocardial contractility.

Echocardiography. All diagnostic ultrasound uses sound waves with a frequency above the audible range to visualize structures (1). Two forms of echocardiography are commonly used today. The most familiar is M-mode or time-motion echocardiography. With this technique, cardiac structures are viewed as if through an ultrasound "ice-pick" inserted through the heart. The M-mode echocardiogram records the motion over time of the cardiac structures in its path on a stripchart recorder. Scans can be recorded by rotating the probe through various cardiac structures.

Two-dimensional echocardiography (2-DE), also called sector scanning, cross-sectional echocardiography, or real-time echocardiography, is the other commonly used form of ultrasonic cardiac imaging (2). The purpose is to record a planar rather than an "ice-pick" view of the heart. This is accomplished by moving the beam either mechanically (sector scan) or electronically (phased-array) through cardiac structures and displaying the result on a video screen. It differs from the M-mode echocardiogram by displaying a two-dimensional image in real-time that can be recorded on videotape.

Different orientations of the heart can be obtained by rotation of the transducer. The most commonly used views in the operating room are the long axis view with an orientation parallel to the long axis of the heart (base to apex), and the short axis view, in which the transducer is rotated 90 degrees from the long axis position. The short axis view at the level of the papillary muscles is used for calculations of area, volume, and ejection fraction by most authors.

M-Mode. M-mode echocardiography is usually applied by cardiologists with a chest wall probe, looking through an "echo window" between the ribs or under the sternum. During cardiac surgery, M-mode echocardiography has been used to obtain left ventricular measurements and function with either retrocardiac (3) or anterior (4) transducer placement. These two methods require placement of a transducer in the operative field and interruption of the surgery to make measurements.

Transesophageal echocardiography (TEE) provides a readily accessible location for continuous cardiac monitoring. The location is stable, monitoring does not interfere with the operation, and monitoring can also be used before the chest is

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opened and after it is closed (5). The technique was initially introduced by Frazin for examination of patients with chronic obstructive pulmonary disease, barrel chests, or obesity who did not have good chest wall "echo windows" (6).

With TEE, recordings can be made at the same location throughout the entire operation and the quality of the image and the resolution of the posterior left ventricular wall are better than that obtained via the chest wall. Another advantage of TEE is that it allows visualization of all structures on the right side of the heart. Most authors have used a 3.5 megaHertz nonfocused esophageal transducer, 10 mm in diameter, with a pulse repetition of 1000 Hertz.

Matsumoto et al used TEE in the M-mode to study 21 patients undergoing cardiac surgery (7). The echocardiogram was recorded at 6 stages during the surgery and compared with simultaneous measurements of cardiac output by dye dilution and filling pressures. They showed that measurement of left ventricular diameter with the TEE correlated very well with measurements made by the standard chest wall method ($r = 0.96$). Left ventricular compliance was found to increase in patients with coronary artery disease after cardiopulmonary bypass; and the ventricular septum was shown to have abnormal motion, possibly due to the lost pericardial restraint. These authors also found a reasonable correlation ($r = 0.72$) between cardiac outputs determined by the echocardiogram and dye dilution techniques.

Controversy still exists as to the accuracy and reliability of using M-mode echocardiographic measurements (single dimension) for quantifying ventricular volume, stroke volume, and cardiac output (8). Despite many theoretical objections to use of M-mode, early studies, as mentioned above, showed good correlation with other measurements.

However, more recent studies have failed to show such good correlation. Rasmussen et al showed the unreliability of M-mode-derived left ventricular dimensions for calculating stroke volume and cardiac output in patients without heart disease (9); certainly these correlations would be worse in patients with cardiac disease and areas of left ventricular asynergy (10). These authors found r values of 0.47 and 0.36 when comparing Fick stroke volumes and cardiac outputs, respectively, with M-mode echocardiographic-derived values.

Among the many reasons these measurements derived from M-mode echocardiograms may not correlate with stroke volume and cardiac output measurements derived from Fick, dye, or thermal dilution are that (a) the left ventricle resembles an ellipse during diastole but not during systole (all formulas are based on an ellipse); (b) the left ventricular wall excursion or thickening is unequal in different regions; or (c) areas of abnormal wall motion due to coronary artery disease or other diseases exist.

Two-Dimensional. Due to the limitation of the M-mode echocardiogram, many investigators are now looking at the usefulness of 2-DE as a continuous monitor of cardiac function. The major advantage of the technique is its ability to visualize an entire cross-sectional slice of the ventricle as opposed to a single linear dimension. It is possible to measure areas of structures seen in cross-sectional image, which allows for estimation of ventricular volumes. Measurements of volume using the long axis view with 2-DE are far superior to those derived from M-mode echocardiograms (11). In addition, areas of poorly functioning ventricle (for example, hypokinetic areas), or abnormal anatomy (for instance, myxomas or aneurysms) can be visualized.

Dubroff et al used a hand-held 2-DE probe directly on the epicardium during cardiac surgery in 44 adult patients (12). Ejection fraction was measured by a short axis area change at the maximum left ventricular cross-section using a Diasonic V-3000, 3.5 megaHertz transducer. This method allowed for rapid assessment of changes in systolic and diastolic parameters during surgery. Ejection fraction derived by this method correlated farily well ($r = 0.85$) with angiographic values. In addition, air was detected emanating from the left ventricle during cardiac surgery in a large number of patients (13).

Two-dimensional TEE with a phased-array transducer was first introduced in 1982 by Schluter et al from West Germany (14). They attached a transducer to a standard gastroscope, allowing for complete control of the tip of the scope. Awake examinations were performed in 26 patients after premedication with diazepam and atropine. Good diagnostic pictures were obtained without complications, and the authors suggested its use an as intraoperative monitor of cardiac function. Since then, numerous investigators have utilized the 2D-TEE probe made by Diasonics during studies in anesthesized patients.

Intraoperative monitoring with the 2D-TEE is a safe and simple procedure which permits continuous assessment of left ventricular volume and contractility. Provided the probe is not moved, relative changes in the left ventricular image can be easily detected. Left ventricular area at the level of the papillary muscles in the short axis view is easily measured, but the calculation of left ventricular volume assumes symmetry which may not always be valid. Therefore, fractional shortening of areas, rather than true ejection fractions, are often calculated as

$$\mathrm{EDA} - \mathrm{ESA}/\mathrm{EDA} \times 100$$

where EDA = end-diastolic area and ESA = end-systolic area.

Anesthetic agents, myocardial ischemia, surgical events, and changes in left ventricular preload or afterload can profoundly affect intraoperative cardiovascular function. Barash (15) and Rathod (16) have shown the effects of inhaled anesthetic agents on echocardiographic measurements. Kremer et al showed with 2D-TEE that changes in left ventricular dimensions occurred in 80% of 16 patients without heart disease undergoing abdominal surgery (17). Immediate improvement of dysfunctioning myocardial segments after coronary revascularization were detected using 2D-TEE by Topol et al (18); and Hinrichs et al showed the value of the 2D-TEE in mechanically ventilated, critically ill patients in the coronary care unit (19).

The less invasive 2D-TEE offers several advantages over a pulmonary artery catheter in patients undergoing major surgery. The true preload of the left ventricle (LVEDV) can be obtained instead of the pulmonary capillary wedge pressure (20). A measurement of contractility (ejection fraction) can be obtained instead of an estimate of cardiac function by the Frank-Starling curve. Finally, and possibly most importantly, early changes of myocardial ischemia may be detected by 2D-TEE. These early changes of decreased compliance and altered wall motion may occur before the appearance of abnormal V waves on the PCWP tracing (21) or ST segment changes on the electrocardiogram.

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Anesthesiology at the Turn of the Century: Where Do We Go From Here?

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It is an honor indeed to have been invited to present the twenty-first Bernard H. Eliasberg Lecture. The title, "Anesthesiology at the Turn of the Century: Where Do We Go from Here?" has not been selected capriciously. Anesthesiology has undergone a spectacular period of growth and maturation over the last 35 years. Especially great have been the changes in the last 15 years. All indications are that the rate of change is not about to slow down, much less cease. Indeed, the rate of change in anesthesiology between now and the year 2004, only 20 years off, may even accelerate as anesthesiology continues to mature. It will also accelerate because of profound changes that are affecting and will continue to affect all of medicine, anesthesiology included.

The genesis of these continuing changes is, in part, biomedical. Witness, for example, what has been happening in pharmacology and physiology in recent years. The genesis of these changes is, however, equally ascribable to profound economic, sociologic, and political/governmental forces that will inevitably affect our future practice.

It behooves us in anesthesiology to consider what some of these changes will consist of. Why? Not, I assure you, for any reason as trivial as the fact that gazing into a crystal ball is a pleasant, if harmless, intellectual exercise. No, the reason we should consider today what is going to happen in anesthesiology between now and the year 2000 is that we can and we must prepare for these changes. The history of anesthesiology has, alas, all too often been characterized by response, passive response, to events and circumstances brought about by others. We have too often been playing catch-up ball. If we are ever going to become masters of our own destiny, insofar as possible, we must anticipate in advance what is likely to happen. And then, having identified what is likely to happen, we must actively set about to influence future changes for our own purposes. If that proves impossible, we must set about adapting to these changes. Forewarned is forearmed.

Here I must—for reasons of space—restrict myself to the major changes that are likely to occur, reviewing them only lightly and relatively without nuance. These likely changes fall into nine categories:

- Areas of clinical responsibility
- Anesthetic techniques
- Pharmacology
- Personnel/manpower
- Economics
- Research funding
- Communication
- Computers
- Epidemiology

Clinical Responsibilities. Two areas of clinical responsibility will be of special importance: the future roles of anesthesiologists in intensive care units and in pain clinics. This is admittedly a difficult subject to address dispassionately and objectively, given the stake that many anesthesiologists now have in intensive care medicine and in the management of patients with chronic pain. Certainly no question whatsoever can arise about the many major contributions that anesthesiologists have made and are continuing to make in these two fields. But what of the future? Can, will, or should anesthesiologists continue to play the role they have played so conspicuously and so

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well in ICUs and pain clinics into the indefinite future?

As far as intensive care is concerned, we already have a situation in which ICUs have proliferated so much and become so specialized that anesthesiologists frequently play little, if any, major role in many of them. Coronary and neonatal care units are examples of ICUs so specialized that, for good and just reasons, they transcend the expertise of most anesthesiologists. The same can also be said for neurologic and neurosurgical ICUs, and perhaps for pediatric ICUs. Specialization in intensive care has so proliferated that anesthesiologists cannot be expert in all areas. The trend to specialization in intensive care will continue and, as it does, anesthesiologists will play a progressively more minor and more restricted role.

But another change is occurring that affects the role of anesthesiologists in ICUs: the development of a generation of physicians trained specificially to be intensivists. Some of these new full-time intensivists come from anesthesiology, some from a variety of other medical specialities. We already have, however—and in the future we will have more and more—full-time intensivists thoroughly and specificially trained and competent in management of patients with trauma, with burns, with ventilatory, renal, cardiac, or hepatic failure, and so on. This new breed of intensivists will gradually but inexorably replace the part-time intensivist based in some other clinical specialty. Surgeons will be increasingly restricted to surgery, anesthesiologists to anesthesia, in much the same way that neonatologists have displaced pediatricians from the care of the high-risk newborn infant.

Much the same can also be said about pain clinics. It is now apparent that the management of patients with chronic pain includes a great deal more than the ability to do nerve blocks. Indeed, nerve blocks are but one part, often a minor part, of a well-run pain clinic. Psychiatrists, neurosurgeons, social service workers, and a host of others are also needed in well-run pain clinics. Again, by the year 2000 it is unlikely that pain clinics will continued to be pseudopods of departments of anesthesiology. Some of the physicians in pain clinics in future years may well have started off as anesthesiologists, but they will increasingly be functioning full-time in separate, autonomous departments.

Anesthetic Techniques. What about anesthetic techniques? Here our crystal ball becomes murky. The half-life of vogues in anesthetic techniques in the past suggests, however, that by the turn of the century the current popularity of industrial doses of narcotics for operative anesthesia (or analgesia, at least) will be on the wane. They will probably still be used, but not as frequently. Inhalation anesthesia will take up some of the slack. So, too, will regional anesthesia. The recent renaissance of regional anesthesia will continue for a few more years until a plateau is reached, a plateau that will continue into the early part of the twenty-first century. The art of local anesthesia provided by the surgeon will continue to deteriorate. By the year 2000 there will be but very few surgeons capable of providing their own anesthesia.

By the year 2000 clinical indications for and the mechanics of high-frequency ventilation will finally become established. High-frequency ventilation will be recognized as a mechanically highly complex technique with definite, albeit infrequent, indications. As such, use of high-frequency ventilation will be limited almost entirely to tertiary care hospitals, but in them high-frequency ventilation will be used relatively often.

Perhaps the most significant changes in techniques will be the further development, refinement, and popularization of techniques for relief of postoperative pain. Anesthesiologists should be the leaders, not the followers, in this field. Relief of postoperative pain will rely increasingly less on intramuscular narcotics. More and more emphasis will be placed on techniques such as transcutaneous electrical stimulation. The role of epidural and intrathecal narcotics will be more completely defined. Epidural and intrathecal narcotics will still be used, but not as frequently as some of their present-day advocates would suggest. New compounds will also be available for long-lasting regional anesthesia for relief of postoperative pain (more about that below). The upshot will be greater patient comfort and a decrease in postoperative morbidity, especially morbidity due to pulmonary complications.

Monitoring techniques are, with one exception, liable to remain basically much as they are today, though undoubtedly with further refinements. The one exception is the likely future availability of methods for continuous intravascular monitoring of blood gas tensions in mixed venous or peripheral arterial blood. Monitoring of somatosensory evoked responses will, because of inherent complexities, probably remain restricted to very special situations.

Pharmacology. What will pharmacology offer us in 2000 AD that will be new? The crystal ball gets even murkier. New inhalation anesthetics may, and probably will be, introduced in the next

15 years. It is hard to believe these agents will represent truly significant pharmacologic advances.

It is quite likely, however, that by the year 2000 a truly short-acting nondepolarizing relaxant will finally be available, one with a duration of action comparable to that of succinylcholine. This will represent a major pharmacologic advance.

Equally likely is the likelihood that new agents will be available that are capable of producing nontoxic, function-specific block of nerve conduction for hours or even days. These agents will not be derivatives of our current local anesthetics, but rather will probably be derivatives of already known biologic neurotoxins such as tetrodotoxin, batrachotoxin, and saxiton. The new compounds will be able to selectively block pain fibers in peripheral nerves without impairment of other somatic sensory fibers or somatic motor fibers. They will revolutionize management of postoperative pain and chronic pain.

Personnel. The number of anesthesiologists will continue its present upward trend both quantitatively and qualitatively for at least the next 20–25 years. The number of graduates of American medical schools will reach a plateau before the year 2000, but the plateau will still turn out new doctors at a rate that exceeds the rate of increase in the population as a whole. The number of physicians will increase. The percentage of physicians entering anesthesiology will also continue to increase.

As the number of physicians in anesthesiology increases, competition will inevitably result in drastic economic changes. Competition will, for one thing, decrease the incomes of anesthesiologists. The increased number of anesthesiologists will also result in translocation of many nurse anesthetics to economically less rewarding urban and rural areas. This, in turn, will bring about a decrease in the number of new entrants into nurse anesthesia.

Economics. The economics of anesthesiology will change because of increased competition. The economics of anesthesiology will also change because of continuation of recently introduced reimbursement schedules based on diagnosis-related groups (DRGs). This is a concept certain to persist in one form or another.

Reimbursement based on DRGs will also force more rigorous and more realistic cost accounting in anesthesiology. Are routine preoperative chest x-rays really necessary for every patient? How cost effective are routine preoperative EKGs for every patient? What preoperative blood chemistries are really needed? Does every operating room really need a hyper-hypothermia unit? Do we really need in all cases all the intraoperative monitors presently used? Is it really necessary to draw up in syringes (and thus waste, if unused) all the drugs that we so often draw up by reflex prior to induction of anesthesia, "just in case?" Fiscal accountability will be introduced. It will force radical alteration of many of our present practices over the next 16 years.

Research Funding. Money for research will continue to be hard to come by. Indeed, it will probably be even harder to obtain by the end of this century. One unhappy result will be that young physicians will be even further alienated from what would appear to be uncertain futures in academic anesthesiology. On the other hand, scarcity of research funding will force a much needed change, closer scrutiny of research that is undertaken. Greater care will be necessary to assure that the research question being addressed is really significant and worthy of financial support, not mere trivial research to fill in minute interstices of knowledge. The paucity of research funds will also force reexamination of how research is supported. One likely result will be greater dependence upon private or commercial philanthropy instead of the National Institutes of Health. An equally likely result will be that clinical faculty in teaching university hospitals will, directly or indirectly, be subsidizing by their clinical practice an increasing portion of the cost of research.

Communication. Communication in anesthesiology, a vital component of the health and strength of the specialty, has two important and closely interrelated goals. One is transmission of information that is new and important, including the results of research. The other is education. At present, these two goals of communication are realized almost entirely by verbal communication and by the printed word. The latter includes anesthesia journals, by which I mean peer-reviewed journals.

Journals have several major advantages as media for communication, some of them unique. Journals can and do simultaneously realize both of the two goals of communication: journals provide the reader with new information, and they educate. The reader can rest assured that the materials in the journals are, by and large, worthy of attention because they have been screened by peer review. Journals also provide information in a permanent and readily accessible form. The materials journals publish can be closely scrutinized. The validity of conclusions drawn can be independently accepted or rejected. Material in print can also be easily retrieved for later study and rereading. Journals are also convenient. They can be read almost anywhere, in one's study, in an airplane, or on the beach. They can be read without the need for any equipment except, for some of us, a pair of bifocals. These are unique attributes. They are shared by neither oral communication nor by electronic media.

The advantages of journals as a means of communication are so manifest and so unique there would appear to be little reason to doubt that journals will still be on the scene and fulfilling their role by the time the year 2000 rolls around. This may not, however, be the case. It may not be the case because of the proliferation of new anesthesia journals. If the rate of proliferation of new anesthesia journals over the last 15 years continues for another 15 years, it is doubtful that many, if any, anesthesia journals will survive into the twenty-first century.

Why? First, an increase in anesthesia journals inevitably leads to fragmentation of published materials. The more fragmented published materials become, the greater the number of journals the reader must subscribe to, to keep up to date. The greater the number of journals one must read, the greater the chance that the journals will either not be read thoroughly or will not be subscribed to. The cost, to say nothing of the inconvenience of trying to keep up with multiple journals, will almost surely increase reader dropout. Keeping up becomes too expensive, too time-consuming, and too confusing.

But there is another and even more important reason why proliferation of anesthesia journals is inimical to communication based upon the printed word. This is the fundamental fact that the amount of material that deserves to be published in anesthesiology is finite. Since the amount of quality material is finite, increasing the number of journals can only be accomplished by filling pages with second-rate material that need not and, indeed, should not even be published in the first place. The stature of any discipline can be judged by the quality of its publications. The dilution of quality published materials by poor materials will detract from the stature of anesthesiology. It will also result in the ultimate demise of journals. Only if the proliferation of journals in anesthesia is checked can one expect the journals in the field to survive into the next century.

Computers. Computers will play increasingly important roles in anesthesiology as the new century draws ever nearer. It is unlikely, though, that every anesthesiologist will need to become an expert in computers to give good, safe anesthesia. More anesthesiologists will, however, need to be fully acquainted with different types of computers. Computers will continue to be needed in research, especially for statistical analyses (a change, incidentally, that will require research anesthesiologists to have much more statistical savvy; the Student's *t* test will no longer suffice). Computers will also be universally used for storage and analysis of data on patients.

Epidemiology of Anesthesiology. The greatest challenge facing anesthesiology at the close of the twentieth century is to establish a truly scientific basis for the clinical practice of anesthesia. At the present time selection of anesthetic agent and technique is, of necessity, based upon clinical judgment, clinical impression, and often dubious pharmacologic and physiologic hypotheses. This comes about because of the absence of any statistical basis for decision-making. Clinical judgment and clinical skills will surely continue to be important in the future. But something as important as choice of anesthetic agent and technique cannot and must not continue to be based on subjective criteria and specious pharmacologic and physiologic reasoning.

We need facts. We need data. All other branches of medicine—with, perhaps, the exception of psychiatry—have developed statistical bases to determine the what, the when, the how, and the why of the medical management they provide. Anesthesiology has, however, not derived statistical or epidemiological data to defend and prove that what we advocate in our clinical practice is, indeed, best for the patient. The most we have at present are data comparing the incidence of phenomena and responses, such as hypotension, changes in pulse rate, nausea and vomiting, and so on, with different agents and techniques. This is not enough.

What we need are epidemiologically sound data to determine the effects of choice of anesthesia on outcome. Outcome is what counts—either morbidity outcome or, better yet, mortality outcome. We do not even have data on such simple, basic questions as what is the best (the safest) anesthesia in terms of outcome for such common operations as elective inguinal herniorrhaphies in adults, TURs, and pneumonectomies. Such data as we do have are either outdated or epidemiologically flawed, or both.

All we have to fall back on is clinical judgment, armchair hypotheses, or, worst of all, the suggestion that clinical skill, not anesthetic agent or technique, is all that really counts. Clinical skill is indeed important, but emphasis placed solely on clinical skill leads to the nihilistic philosophy that it doesn't make any difference what one does, it's how well one does it. Surely the pharmacology of drugs used in anesthesia makes a difference. To deny this makes the choice of anesthetic agent a travesty.

The reason we do not have data to defend our choices of anesthetic agents and techniques lies, of course, in the monumental complexities involved in deriving such data. Just to prove whether spinal or general anesthesia is better in terms of outcome for elective inguinal herniorrhaphies in adults would be a horrendously complicated study. Patients would have to be randomly assigned prospectively to receive either spinal anesthesia or one of three or four standardized types of general anesthesia. Since anesthetic deaths are so infrequent, several thousand patients would have to be studied, all free of complicating concurrent diseases, all provided with anesthesia administered with equal skill, and all subjected to standardized follow-ups. Another study would then be necessary to determine the best anesthetic management, in terms of outcome, for patients having inguinal herniorrhaphies with complications such as obesity, hypertension, asthma, and so on. Comparable data would also then have to be derived for other operations, from coronary artery bypass, to craniotomies, to cholecystectomies.

Studies such as these require prospective multi-institutional participation over a period of many, many years—a mind-boggling prospect indeed, but not insurmountable. Others have done it. Look at the Framingham study. Look at the multi-institutional studies of the management of hypertension, angina, myocardial infarction, infectious diseases, and diabetes, to name just a few. We in anesthesiology can do the same thing. We must do the same thing. If we don't, we can hardly blame those outside anesthesiology for continuing to believe that anesthesia really plays little significant role in outcome.

We know anesthesia does make a difference. We must prove it. We must prove it in epidemiologically acceptable terms. That is the challenge for anesthesiology in the twenty-first century: quantitation of anesthetic risk; quantitation of methods to decrease risk. There is little doubt that, difficult though such data will be to obtain, they will be obtained, gradually but inexorably.

As such data are obtained, placing selection of anesthetic agents and techniques on a statistically sound basis will have the side effect of forcing anesthesiologists to become really complete anesthetists, equally competent in and comfortable with all anesthetic agents, not just a few, not just those that are easiest, most convenient, and most readily learned. In the twenty-first century, anesthesiologists will increasingly need to become masters of many techniques, regional as well as general, not just one or two techniques. Anesthesiologists will become masters of many techniques because they will be obliged to defend their choice of agent and technique on objective data-based grounds, not on the grounds of clinical impression.

The Mount Sinai Journal of Medicine
Awards 1983/1984
Presented at Awards Ceremony June 1, 1984

THE MOUNT SINAI JOURNAL OF MEDICINE
Vol. 51, No. 5, September, 1984
Printed in U.S.A.

Journal Awards 1983/84

Student Prize

Marta Rico, Ph.D., M.D.

The 1983/84 Student Prize has been awarded to Marta Rico, Ph.D., M.D., for "Breast Cancer: Risk Factors and Etiology" (vol. 51, no. 3), written when the author was a third-year student at Mount Sinai School of Medicine (CUNY). The author has a B.S. degree awarded by the University of Puerto Rico and a Ph.D. in genetics from Yale University. She begins her residency in internal medicine at The Mount Sinai Hospital in 1984. The Student Prize, established in 1971, is awarded to encourage students—the group from which future leaders of medicine may come—to explore the publication process.

Ralph Colp Award

Robert J. Greenstein, M.D., has received the 1983/84 Ralph Colp Award for his paper "Selective Gastrointestinal Circulatory Changes due to a Vasopressin Hormonogen in the Cat" (vol. 50, no. 6), written with David A. Dreiling, M.D., who declined to receive this award because of his senior status. The Ralph Colp Award was established by colleagues and friends of Dr. Colp, distinguished surgeon and long-time chief of surgery of The Mount Sinai Hospital. Preference is given to, but is not restricted to, papers on surgical matters written by junior members of the Department of Surgery at the Hospital.

Globus–Mount Sinai Journal Award

The Globus–Mount Sinai Journal Award is named for Joseph H. Globus, founding and first editor-in-chief (1934–1952) of the *Journal.* The award is for the best paper with a clinical orientation published during the academic year. The award was not given in 1983/84.

General Articles, Specialty Notes, And Letters

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The Low-T_3, Low-T_4 Syndrome of Nonthyroidal Illness: Adaptive Temporary Hypothyroidism

Barnett Zumoff, M.D.

Abstract

The studies that have defined the thyroid hormonal abnormalities of nonthyroidal illness (NTI) are reviewed. Initially it was reported that plasma T_3 levels were decreased in the face of normal T_4 and TSH levels. This "low-T_3 syndrome" was felt to be due solely to diminished peripheral conversion of T_4 to T_3. More recently it has been found that a subset of NTI patients have decreased plasma levels of free T_4 as well as T_3. This indicates that these patients have diminished thyroidal secretion of thyroxine, which is hypothyroidism by definition. Various studies have shown that such NTI patients manifest a number of hormonal, biochemical, and physiological stigmata of hypothyroidism. It is proposed that patients with the "low-T_3, low-T_4 syndrome" of nonthyroidal illness do indeed have adaptive, temporary hypothyroidism, as part of a generalized adaptation to the stress of illness. Thyroid hormonal therapy of such patients is believed to be inappropriate and undesirable, unless they have known prior hypothyroidism, unequivocal physical findings of hypothyroidism, or otherwise unexplained coma that has the clinical features of myxedema coma.

The first report that many patients with severe nonthyroidal illness (NTI) had subnormal plasma and tissue levels of triiodothyronine (T_3) was published by Reichlin et al in this journal just 11 years ago (1). These findings were soon confirmed widely, stimulating intense investigational activity concerned with defining the nature and clarifying the pathophysiology of what we (2) and others came to call the "low-T_3 syndrome." The concepts have evolved through several stages, and it is my purpose here to review this evolution and present a view that appears to me to be a reasonable synthesis of the current state of knowledge.

Peripheral Dysmetabolism Hypothesis. Though there had been several earlier reports (3, 4) of subnormal plasma levels of protein-bound iodine (PBI) and thyroxine (T_4) in NTI patients, the earliest papers after Reichlin's quite uniformly reported that plasma levels of T_4 were normal despite the low T_3 levels (5–8). This combination of findings led to the hypothesis that the operative pathophysiology was diminished peripheral conversion of T_4 to T_3 (9, 10).

A further elaboration of this peripheral dysmetabolism hypothesis involved the role of "reverse T_3" (rT_3), a substance produced by inner-ring monodeiodination of T_4 rather than the outer-ring monodeiodination that produces T_3. Levels of rT_3 were reported (11) to be normal or elevated in patients with low-T_3 syndrome, and it was initially postulated that the $T_4 \rightarrow T_3$ and $T_4 \rightarrow rT_3$ reactions were metabolic alternatives, with decreased formation of T_3 in sick patients compensated for by increased formation of rT_3 (12). However, subsequent studies (13) showed that the maintenance of normal or elevated rT_3 levels in NTI patients was a result of diminished metabolic removal in the face of essentially normal production. In any case, the then-reported constellation of findings in NTI patients, namely low T_3 levels, normal T_4 levels, normal or ele-

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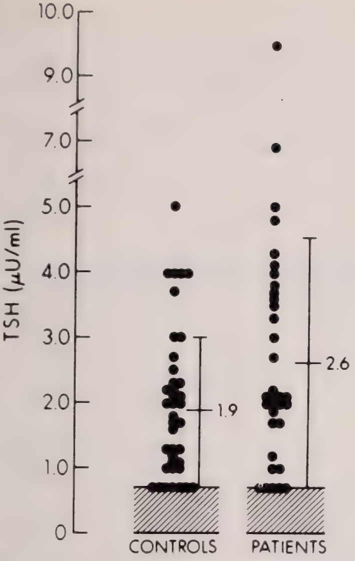

Fig. 1. Plasma TSH levels in controls and NTI patients. Though overlap is considerable the mean value for the NTI patients is significantly elevated. Reprinted, with permission, from Bernstein and Oppenheimer (4).

vated rT_3 levels, and normal TSH levels (14), was considered to represent a condition quite different and easily distinguishable from hypothyroidism.

The putative absence of elevated TSH levels in the presence of low plasma T_3 levels was considered puzzling, and was variously accounted for by postulating either that TSH secretion was regulated by plasma T_4 levels rather than T_3 levels (15) or that NTI patients had an additional defect of hypothalamic-pituitary function that inhibited the expected negative feedback increase in TSH secretion in response to decreased plasma thyroid hormone levels (16).

Largely overlooked in this discussion was the fact that the earliest comprehensive published study of the pathophysiology of the low-T_3 syndrome (5) had reported that TSH levels were indeed somewhat elevated in NTI patients as a group (Fig. 1), and that these patients also manifested clear, if modest, hyper-responsiveness to stimulation with thyrotropin-releasing hormone (TRH) (Fig. 2). Mild elevations of plasma TSH levels, generally up to 20–25 μU/ml but occasionally up to as high as 60 μU/ml (17), have continued to be reported in NTI patients (17–20); presumably these elevations would be even greater if it were not for the fact that NTI patients have sluggish feedback response of TSH secretion to lowering the plasma levels of thyroid hormones (21).

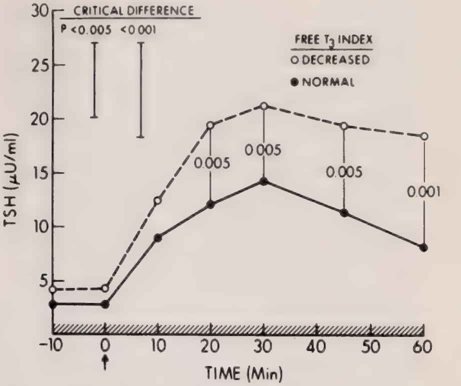

Fig. 2. TSH response to TRH stimulation in controls and NTI patients. Patients' response is significantly greater. Reprinted, with permission, from Bermudez et al (5).

Thus plasma TSH levels do not, in fact, constitute a clearcut and reliable parameter by which to distinguish the low-T_3 syndrome from hypothyroidism in all cases. The same is true of plasma rT_3 levels, since it has been reported that they are sometimes normal in clearly hypothyroid patients (22), presumably because of slowed metabolic clearance that counterbalances the diminished production, and are sometimes low in NTI patients (17, 23).

Low T_4 Levels Rediscovered. Not long after the first description of the low-T_3 syndrome, several groups (24, 25) "rediscovered" that NTI patients in this category sometimes, though not always, had subnormal plasma levels of T_4 as well. This observation was soon widely confirmed (16, 26, 27). It was now necessary to describe the thyroid hormonal abnormalities of this subset of NTI patients as the "low-T_3, low-T_4 syndrome." The fact that the levels of both hormones were subnormal implied that thyroidal secretion of thyroxine was subnormal, which, by definition, constituted hypothyroidism. This focused the attention of researchers and clinicians in this field on the problem of distinguishing the thyroid hormonal abnormalities of such NTI patients from those of "real" hypothyroidism.

Initially, it appeared that a clear distinction did exist, since it was reported (22, 28) that the NTI patients had normal levels of free (non-protein-bound) T_4 despite the subnormal levels of total T_4, in contrast with hypothyroid patients, in

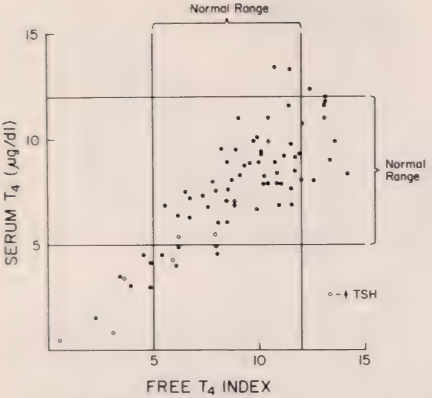

Fig. 3. Relationship between total plasma T_4 and free T_4 levels in NTI patients. Relationship is essentially linear throughout; TSH levels are elevated in nearly half of patients with low T_4 values. Reprinted, with permission, from Gooch et al (17).

whom both free and total T_4 levels were subnormal. However, it was soon reported (16, 17, 19) that free T_4 levels too were often subnormal in NTI.

This led to a literature controversy about the analytical methodology for determination of free T_4. Chopra et al (29) claimed that the reportedly low free T_4 levels in NTI were artifactual, and that the "best" method of determining free T_4, namely equilibrium dialysis, yielded normal free T_4 levels even when less satisfactory (in their opinion) methods showed subnormal levels. However, Melmed et al (19) found that all methods of determining free T_4, including equilibrium dialysis, gave quite comparable values, which were frequently subnormal in NTI patients. Gooch et al (17) reported an extremely interesting and important fact, that the plasma levels of free T_4 and total T_4 showed a highly significant linear correlation over a very wide range of subnormal, normal, and occasionally supranormal levels in NTI patients (Fig. 3); statistically speaking, therefore, the level of free T_4 conveyed no additional independent information beyond that provided by the total T_4 level.

At this point, the distinction between the low-T_3, low-T_4 syndrome and clinical hypothyroidism was blurring, since the NTI patients appeared not to differ qualitatively in any reliable, clearcut way from hypothyroid patients with respect to thyroid hormonal parameters; T_3, total T_4, and free T_4 were frequently subnormal in NTI, TSH was often modestly elevated, and the TSH response to TRH could be supranormal. The distinction came to depend chiefly on the putative absence of clinical, biochemical, and physiological stigmata of "real" hypothyroidism in NTI patients.

The absence of clinical stigmata provides only an insecure parameter, since the clinical picture may sometimes be far from obvious or typical in even unequivocal hypothyroidism, especially when it is of relatively short duration, like the illness of some NTI patients.

Biochemical stigmata of hypothyroidism (other than the plasma thyroid hormonal levels) are few and subtle (30). Two such stigmata, namely diminished 5α-reduction of androgenic steroids (31) and elevation of the urinary tetrahydrocortisol/tetrahydrocortisone ratio (32), are in fact present in NTI patients (2, 33); two others, namely subnormal levels of mitochondrial α-glycerophosphate dehydrogenase and subnormal levels of cytosolic malate dehydrogenase, are present in uremic rats with low T_3 levels (34).

As for physiological stigmata, a very recent report (35) clearly demonstrates that prolongation of the pulse arrival time (Q_kD), a finding generally considered diagnostic of clinical hypothyroidism (36), also occurs in acute starvation, which is an accepted experimental paradigm of the low-T_3 syndrome.

No Distinction Necessary. How then are we to make the distinction between the low-T_3, low-T_4 syndrome and "real" hypothyroidism? I suggest that the reason we have so much trouble making this distinction is that there is none—the low-T_3, low-T_4 syndrome is, in fact, a form of hypothyroidism; specifically, it is adaptive, temporary hypothyroidism.

The concept that adaptive, temporary alterations of hormone secretion take place in acute or chronic NTI is well established with respect to cortisol. Many types of ill patients, including but not limited to those in postoperative and postburn states (37) and those with uremia (38, 39), prostate cancer (40, 41), anorexia nervosa (42, 43), and psychotic depression (44, 45), have hypercortisolemia and increased cortisol production. In several of these conditions it has also been shown that the increased cortisol production is resistant to suppression by dexamethasone (38, 42, 45).

The major diffference between NTI patients and those with Cushing's syndrome is that the abnormalities in the former go away when the patient gets better (43, 44). So, too, does the decrease in T_3 and T_4 levels in NTI patients go away when they get better (5, 14, 18); see Fig. 4.

That the decrease in T_3 and T_4 levels in NTI

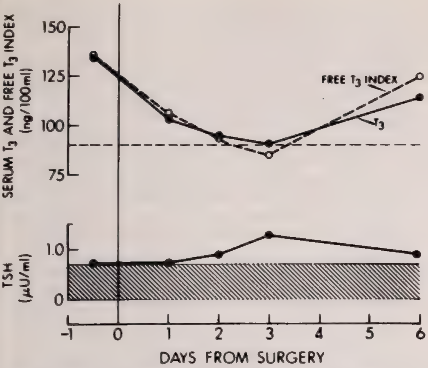

Fig. 4. Time of plasma T_3 and TSH levels after surgery. Reprinted, with permission, from Bermudez et al (5).

patients is adaptive has been suggested by many workers (9, 14, 35, 46, 47). The concept usually proposed is that the lowering of the hormone levels results in diminution of tissue metabolic demand during a period of stress, and that this protects the tissues (14, 46, 47). On theoretical grounds, therefore, treatment of NTI patients with thyroactive substances might be harmful. Experimental studies (46, 48–50) support this assumption, since administration of restorative doses of thyroid hormone to experimentally starved persons whose T_3 levels have become subnormal accelerates protein and fat catabolism, as manifested by increased gluconeogenesis, increased excretion of urea, creatine, and 3-methylhistidine, and elevated plasma levels of free fatty acids and ketone bodies. Such changes could hardly fail to be detrimental to ill patients. This being the case, making the distinction between the low-T_3, low-T_4 syndrome and clinical hypothyroidism is important if it is going to affect the decision about whether to treat the patient with thyroid hormone.

Guidelines. I should like to propose some guidelines for dealing with NTI patients with low T_3 and free T_4 levels. Three basic principles inform these guidelines: first, that hypothyroidism, while uncomfortable and unpleasant for the patient, is not a medical emergency and is not life-threatening except in the case of myxedema coma; second, that the advent of recovery will clarify the situation, since the low-T_3, low-T_4 syndrome will normalize whereas clinical hypothyroidism will not; third, that thyroid hormone therapy might aggravate the clinical state of NTI patients or even increase their mortality rate, an admittedly unproven possibility but a worrisome one. It follows, I believe, that NTI patients with low plasma T_3 and free T_4 levels should not be treated with thyroid hormone except when either (a) there is a documented history of prior hypothyroidism and an indication that the patient may have omitted replacement thyroid hormone for some time; (b) the patient has classical and unequivocal physical findings of severe hypothyroidism; or (c) the patient is in coma, otherwise unexplained, and has features suggestive of myxedema coma, such as hypothermia, depressed respiration, and hypercapnea.

Whether this is the right approach can only be decided by future experience. One possibility is that NTI patients may turn out to require different approaches to their low-T_3, low-T_4 syndrome depending on the specific diagnosis. A possible example is the recent report (51) that the presence of hypothyroidism adversely affects the outcome of an experimentally induced "evolving myocardial infarction" in dogs; given a patient with an analogous condition (unstable angina or early or extending infarction) and low T_3 and free T_4 levels, it might be desirable to treat him or her with thyroid hormone more freely, with less restrictive criteria than those outlined above, because the benefits of treating possible hypothyroidism might outweigh the metabolic and cardiac risks of treating a patient with the low-T_3, low-T_4 syndrome who is not clinically hypothyroid.

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Anesthetic Management of a Patient with Osler-Weber-Rendu Disease and Chronic Renal Failure

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Abstract

The anesthetic management of a patient with Osler-Weber-Rendu disease is described. Osler-Weber-Rendu disease is characterized by telangiectatic mucosal lesions, visceral telangiectases, and pulmonary arteriovenous fistulae. Potential anesthetic complications relate to bleeding from mucosal telangiectases, iron deficiency anemia, hypoxemia, and high output cardiac failure. In this case coexisting renal failure was the major factor influencing anesthetic management.

Osler-Weber-Rendu disease, also known as hereditary hemorrhagic telangiectasia, is a rare inherited autosomal dominant disorder manifested by a widespread developmental abnormality of the vasculature (1–3).

Clinical features of particular interest to the anesthesiologist relate to the occurrence of mucosal telangiectatic lesions and pulmonary arteriovenous fistulae. Severe bleeding from telangiectatic lesions in the oropharynx may follow airway insertion or laryngoscopy and endotracheal intubation. Additional complications of this disease include anemia, hypoxemia, and high output cardiac failure (4).

In the case described, chronic renal failure, unsuspected mitral regurgitation, and coronary artery disease were also present. The anesthetic management of this patient therefore entailed consideration of complications relating not only to Osler-Weber-Rendu disease (OWR), but also to coexisting renal and cardiac disease.

Case Report

A 59-year-old 62-kg man developed bilateral sphenopalatine artery embolization. He was known to have OWRD, and his severe recurrent epistaxis had required transfusion of 75 units of blood over 5 years; congestive heart failure occurred during rapid transfusion on several occasions. Three and a half years before, arterial vessels feeding telangiectatic lesions in his nose were embolized with absorbable gelatin sponge (Gelfoam), but relief was only transient.

As a child, the patient underwent a right nephrectomy following trauma. He was known to have severe hypertension and renal tubular acidosis for three to four years. Sodium polystyrene sulfonate (Kayexalate cation exchange resin) was given for hyperkalemia, but despite deteriorating renal function, he had not undergone dialysis.

Eleven days prior to anesthesia, he developed severe epistaxis necessitating hospitalization. On admission, his hemoglobin was 9 gm%, BUN 155 mg/dl, and creatinine 9.4 mg/dl.

Arterial embolization with polyvinyl alcohol foam, a more permanent material than Gelfoam, was planned. An initial attempt with local anesthesia and intravenous sedation failed because the patient did not cooperate. His request for general anesthesia was declined because of his electrolyte and acid-base abnormalities, BUN of 187 mg/dl, and creatinine of 9.7 mg/dl. The patient refused to undergo dialysis. After five days of severe continuous epistaxis, he finally agreed to hemodialysis, which was performed on the evening prior to surgery.

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Physical examination preoperatively revealed blood pressure of 160/90 mmHg, heart rate of 70/minute, and respiratory rate of 22 breaths per minute. On auscultation, the lungs were clear. Heart sounds were regular, with a grade 1/6 diastolic murmur at the left sternal border, and no S_3 or S_4 gallop. Jugular venous distention was not present. There were numerous telangiectases on the nose, and both nares were packed with gauze. No telangiectases were visible in the oropharynx.

His medical regimen consisted of isosorbide dinitrate (Isordil) 40 mg every four hours, metoprolol tartrate (Lopressor) 100 mg three times a day, clonidine hydrochloride (Catapres) 0.1 mg daily, sodium bicarbonate 1300 mg three times a day, ferrous sulfate 300 mg twice a day, and sodium polystyrene sulfonate (Kayexalate) cation exchange resin 15 gm every other day.

Preoperative (postdialysis) laboratory data were Na^+ 133 mEq/l, K^+ 4.6 mEq/l, Cl^- 110 mEq/l, CO_2 11 mEg/l, BUN 117 mg/dl, glucose 187 mg/dl, creatinine 7.5 mg/dl, alkaline phosphatase 379 mu/ml, Ca^{++} 7.1 mg/dl, P 7.1 mg/dl, albumin 2.4 gms/dl. Arterial blood gases with the patient breathing room air showed pH 7.35, $PaCO_2$ 16.1 mmHg, PaO_2 131 mmHg, and base deficit 13 mEq/l. Chest x-ray was normal. EKG showed normal sinus rhythm, left ventricular hypertrophy, and nonspecific ST-T wave changes.

On the day of surgery he received his usual morning doses of isosorbide dinitrate, metoprolol tartrate, and clonidine hydrochloride with sips of water. Premedication consisted of lorazepam 3 mg intramuscularly 30 minutes prior to arrival in the neuroradiology suite. Immediately prior to induction, blood pressure was 220/100 mmHg, heart rate 62 beats per minute, and respiratory rate 20 breaths per minute. After the insertion of 18 and 20 gauge venous catheters and a 20 gauge radial artery catheter, his baseline arterial blood gases were pH 7.35, $PaCO_2$ 21 mmHg, PaO_2 113 mmHg, and base deficit of 13 mEq/l.

Anesthesia was induced with 250 mg thiamylal and 100 mcg fentanyl. Following ventilation with 100% oxygen, d-tubocurarine was administered in incremental doses to a total dose of 45 mg, followed by 100 mg of lidocaine intravenously. The trachea was intubated without difficulty using a lubricated 8.0 mm Portex endotracheal tube, and thereafter ventilation was controlled. Following an uneventful induction, a 7.5 Fr thermistor tipped, flow-directed (Swan-Ganz) catheter was inserted percutaneously via the right internal jugular vein. An Edwards Laboratory computer was used to determine cardiac output by the thermodilution technique. Pulmonary artery pressures were elevated: systolic 59, diastolic 30 mmHg, and pulmonary capillary wedge pressure 29 mmHg.

Anesthesia was maintained with 60% nitrous oxide, incremental doses of fentanyl and d-tubocurarine, and small supplemental doses of isoflurane. Arterial blood pressure 15 minutes postinduction was 180/100 mmHg, heart rate was 62 beats per minute, and arterial blood gases were pH 7.33, $PaCO_2$ 20 mmHg, PaO_2 115 mmHg, and base deficit 14 mEq/l.

During the 7-hour procedure, blood pressure was maintained in the range 150–160/80–90 mmHg. Occasional elevations above this level were rapidly controlled with low concentrations of Isoflurane but were associated with the appearance of giant V waves on the pulmonary capillary wedge pressure (PCWP) tracing. PCWP varied between 30 and 35 mmHg, and cardiac output between 3.5 and 4 l/minute. The heart rate varied between 55 and 65 beats/minute. Throughout the EKG remained stable, with no ST-T depression and with no arrhythmias. Atropine 0.2mg intravenously was administered on two occasions when the rate fell below 60. Arterial blood gases were determined hourly and consistently indicated respiratory alkalosis and metabolic acidosis. Sodium bicarbonate 200 mEq was administered in 50 mEq increments; the final acid base determination showed pH 7.44, base deficit 10 mEq/l, $PaCO_2$ 17.3 mmHg, PaO_2 143 mmHg.

The procedure was completed with difficulty. An introducer sheath was inserted into the left femoral artery, a catheter advanced easily into the left sphenopalatine artery, and polyvinyl alcohol foam (PVA) injected to occlude the artery. Multiple attempts at the cannulation of the right sphenopalatine artery were unsuccessful, and therefore a direct right carotid cannulation was performed. The right sphenopalatine artery was successfully cannulated via the right carotid, and PVA was injected. Following right carotid puncture a hematoma developed in the right side of the neck. At the conclusion of the procedure, pressure was applied to the right neck for 15 minutes, after which the hematoma which was present did not appear to be expanding. Nevertheless, the trachea was kept intubated to avoid compromise of the airway.

The patient was transferred to the surgical intensive care unit and placed on mechanical ventilation. Soon after arrival in the intensive care unit, his blood pressure rose to 230/110 mmHg.

This hypertensive episode was unresponsive to therapy with intravenous nitroglycerin 200 micrograms/minute, responded poorly to intravenous sodium nitroprusside (Nipride) 500 micrograms/minute, and persisted for several hours.

Chest x-ray that evening showed mediastinal widening, secondary to blood tracking down from the neck hematoma. An emergency arch aortogram and right carotid angiogram demonstrated a leak from the right carotid puncture site. This necessitated emergency exploration of the right side of the neck and repair of the right carotid arteriotomy.

Anesesthesia for this procedure was uneventful, and consisted of 50% nitrous oxide, incremental doses of fentanyl, and 0.5% isoflurane. The surgical procedure was performed without complication.

Upon return to the intensive care unit, the patient remained hypertensive, but was more responsive to sodium nitroprusside. During the course of the first postoperative day, the blood pressure decreased to preoperative levels. His initial postoperative course was uneventful, he was extubated on the fourth postoperative day, and discharged from the intensive care unit on the fifth postoperative day. No further epistaxis occurred.

During the course of the next week, he became progressively more uremic but nonetheless continued to refuse dialysis. On the eighth postoperative day he suffered a grand mal seizure, which was believed to be secondary to uremia and acid-base and electrolyte abnormalities. At that time, he finally agreed to undergo dialysis, but despite dialysis continued to have seizures. Subsequently septicemia developed, and on the tenth postoperative day he was transferred to the medical intensive care unit. He died on the eleventh postoperative day and was thought to have suffered a myocardial infarction.

Postmortem examination of the heart revealed only an old anterior wall infarction, calcific sclerosis of the mitral annulus, and severe coronary artery disease. Examination of the remaining left kidney showed arterionephrosclerosis, an old cortical infarct, and atrophy and stenosis of the ureter.

Discussion

The mucosal telangiectatic lesions of Osler-Weber-Rendu disease most commonly occur in the nose, but may also be present on the lips, gums, tongue, palate, and epiglottis and in the larynx, trachea, or bronchi (1, 4). In this case, lesions were identified in the nasal mucosa only but, as a precaution, laryngoscopy and endotracheal intubation were performed in a circumspect manner.

Epistaxis may be of great severity and its chronicity may be debilitating; the resulting iron deficiency anemia is a common complication (5).

Of the visceral telangiectases associated with the disease, pulmonary arteriovenous fistulae are of major interest. These are often multiple and responsible for significant shunting and consequent hypoxemia and high output cardiac failure. Pulmonary arteriovenous fistulae occur in 15% of patients with the disease, but the preoperative chest x-ray of this patient did not reveal the rounded homogenous masses of consistent density characteristic of such lesions (4, 5).

Polycystic kidney, an occasional feature of Osler-Weber-Rendu disease, was not present in this patient (5).

Mitral regurgitation, which was diagnosed intraoperatively, was presumed due to dilatation of the mitral valve secondary to left ventricular hypertrophy. Vasodilator therapy, to reduce systemic vascular resistance and left ventricular end diastolic pressure and improve forward left ventricular stroke volume, was considered and nitroglycerin made ready. The possibility that the V waves and elevated PCWP were early signs of myocardial ischemia, as described by Kaplan and Wells (6), was also considered. However, as systemic blood pressure largely remained in the preoperative range an expectant approach was adopted and nitroglycerin was not administered during the procedure.

The significance of electrolyte and acid-base disorders is well appreciated but the choice of anesthetic agents for patients with marked impairment of renal function is less well defined.

Barbiturates are acceptable as induction agents but need to be administered cautiously. An exaggerated response due to decreased protein binding and deficiencies in the integrity of the blood brain barrier may occur in uremic patients (7). Profound hypotension may follow intravenous barbiturates because such patients are—or respond as if they are—hypovolemic (8).

The hyperkalemic response to succinylcholine is of concern in uremic patients, but the use of succinylcholine is acceptable provided that serum potassium levels are neither above the normal range nor at the high normal level (8). We elected to employ a nondepolarizing relaxant both during the procedure and to facilitate endotracheal intubation, thereby avoiding such considerations.

The elimination of atracurium and vecuronium is dependent on nonrenal mechanisms and these agents, not yet widely available, would appear to be the muscle relaxants of choice for patients with diminished renal function (9, 10). In contrast, the elimination of gallamine and metocurine is largely dependent on renal excretion and their use is contraindicated in such circumstances (11). Our choice was limited to d-tubocurarine or pancuronium. D-tubocurarine was preferred despite its hypotensive effects because its elimination is less dependent on renal excretion compared to pancuronium (11–13). However, if mitral regurgitation has been suspected preoperatively, pancuronium might have been preferred, because the mild increase in heart rate produced by this drug would have been beneficial by increasing forward left ventricular stroke volume, whereas the magnitude of reduction in systemic vascular resistance with d-tubocurarine is unpredictable. Of the volatile agents, isoflurane, little metabolized and associated with cardiovascular stability, appears the most suitable.

The severity of nasal hemorrhage in this case was deemed life-threatening. Interspeciality consultations led to a consensus of opinion that sphenopalatine embolization was the therapeutic measure of choice and that the hazards associated with renal failure and hypertension unavoidable.

This patient, however, despite psychiatric counseling and repeated explanations of risk factors, was extremely reluctant to undergo renal dialysis and adamant in refusing to undergo embolization other than with general anesthesia. He indicated repeatedly that he preferred death rather than dialysis or embolization with local anesthesia, and thereby provoked many ethical and moral issues. Ultimately, he consented to undergo dialysis once. Preoperative electrolyte levels were within normal limits, but urea and creatinine levels were still markedly elevated.

In summary: the anesthetic management of a patient with a rare condition (OWRD) in which the principle concerns are hemorrhage and anemia and are relatively routine was made hazardous by coexisting cardiac and renal disease.

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Infective Endocarditis in Hypertrophic Cardiomyopathy: Case Report and Review of Literature 1961–1982

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Abstract

Infective endocarditis in patients with hypertrophic cardiomyopathy is infrequently reported, though it may not be uncommon. A case of infective endocarditis in which *Streptococcus viridans* was isolated from the skin and blood cultures is described in a patient with hypertrophic obstructive cardiomyopathy. The primary event leading to bacteremia and endocarditis was a skin reaction to antiarrhythmic treatment with amiodarone.

An analysis of the 39 documented cases of infective endocarditis among approximately 500 patients with hypertrophic cardiomyopathy during the years 1961–1982 is presented. Particular attention is given to the site of infection, type of bacteria, precipitating causes, and mortality rate.

In the majority of cases mitral regurgitation and a large intraventricular gradient were found. Endocarditis can involve the aortic or the mitral valve, or both in the same event. The commonest recognized etiologic agent was *S. viridans*. From a review of the data it is clear that in patients with hypertrophic obstructive cardiomyopathy, preventive treatment for infective endocarditis is mandatory.

Infective endocarditis in patients suffering from hypertrophic cardiomyopathy, also known as idiopathic hypertrophic subaortic stenosis, is infrequently reported, and disagreement on the prevalence of this serious complication is evident in the literature. From 1961 to 1982, 39 well-documented cases of infective endocarditis were described in more than 500 reported patients with hypertrophic cardiomyopathy.

We present the case of a patient with hypertrophic cardiomyopathy complicated by infective endocarditis. The primary event that caused infective endocarditis was a rare skin reaction to amiodarone treatment. The skin reaction was a vasculitic lesion which converted to pustules after secondary infection with *Streptococcus viridans*. The same etiologic factor was isolated from the blood. The unusual nature of this case prompted us to record it.

Case Report

A 57-year-old white man was admitted to the hospital because of fever and progressive weakness. He had been well until 19 years before his present admission, when he was referred to a cardiology clinic for evaluation of mild hypertension and a cardiac murmur which were found on a routine check-up.

At that time (when he was 38 years old), his blood pressure was 130/80 in both arms; his pulse was regular at 74/min. The point of maximal impulse was at the fifth left intercostal space, between the mid clavicular and anterior axillary lines. An apical presystolic wave was palpated and a fourth heart sound was heard at the apex. A paradoxical splitting of the second heart sound was found at the left sternal border. A systolic

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ejection murmur, grade 2/6, was heard maximally at the fourth intercostal space to the left of the sternum, radiating to the base and apex of the heart. The murmur became louder and regurgitant during a Valsalva maneuver. Chest x-ray revealed cardiomegaly without evidence of congestive heart failure. The electrocardiogram showed left ventricular hypertrophy, left atrial abnormality, and abnormal Q waves in leads I, II, V_{2-6}.

Seven years before the present admission, the patient noticed a gradual decrease in exercise tolerance. An echocardiogram performed at this time revealed an interventricular septum of 16 mm and posterior wall thickness of 14 mm; the left ventricular diameter was 24 mm, the left atrial diameter 60 mm. Evidence of systolic anterior movement of mitral leaflet was found, with a calculated peak systolic gradient of 93 mmHg. Treatment with propranolol was started.

One year before the present admission the patient complained of dyspnea on exertion, dizziness, severe fatigue, and recurrent palpitation. His neck veins were distended to the angle of the jaw at 40° and prominent jugular venous "A" waves were present. A third and fourth heart sound were found at the apex, and the murmurs described on previous examinations were heard. Chest x-ray revealed pulmonary venous hypertension and Kerley B lines. Electrocardiogram and vectorcardiogram yielded signs of right atrial and right ventricular hypertrophy in addition to the changes noted previously. Holter monitoring revealed paroxysmal atrial fibrillation and multiple premature ventricular beats. On repeated echocardiogram there was an increase in the thickness of interventricular septum from 16 to 19 mm, and in the calculated peak systolic gradient at rest from 93 to 125 mmHg. Treatment with propranolol was continued; furosemide and quinidine were added. The quinidine was stopped two weeks later because of diarrhea, and amiodarone 400 mg/day was started.

Three months later he noted multiple bullous lesions on both legs. Most of them broke and became pustular, and the patient complained of low-grade fever. The initial skin changes were typical of a vasculitic lesion.

Cultures from the pustules revealed growth of *S. viridans*. The diagnosis was skin reaction to amiodarone, and the drug was stopped. His skin lesions persisted for 3 weeks after discontinuing the drug and then slowly resolved without medical treatment. Four weeks after the appearance of the cutaneous manifestations the patient complained of an evening fever up to 39° without chills, with profuse sweating, palpitations, progressive weakness, loss of appetite, and loss of weight. He was hospitalized. On admission his temperature was 37.0–38.8°C, his blood pressure was 85/60 mmHg, his pulse was regular at 72/min, and his respiratory rate was 20/min.

He had 2 petechiae on the pulp of his fingers, one on a toe, and one on his soft palate. Urine examination revealed microscopic hematuria. Chest x-ray revealed no evidence of congestive failure.

Laboratory examination results were as follows: hemoglobin 9.5 gr%, hematocrit 28%, white blood cell count 7400 with shift to the left. The C_3, C_4, anti-DNA, latex test, and VDRL were negative. T_4 was 13.8%, T_3 49%; thyroid uptake with ^{131}I was 3% after 24 hours, results compatible with amiodarone treatment. Tests for Widal, Weil-Felix, and *Brucella* were negative.

M-mode echocardiogram revealed no evidence of vegetations.

On the second day of admission rapid atrial fibrillation appeared, electrical cardioversion was performed, and treatment with disopyramide (600mg/d) was started; later, verapamil was added, in a dose gradually increasing to 480 mg/d.

On the third day of admission blood cultures positive for *S. viridans,* with antibiotic sensitivity identical to that of the *Streptococcus* cultured from the skin lesions, confirmed the presumptive diagnosis of infective endocarditis. Intravenous treatment with penicillin was started at a dose of 20 million units per day.

After 3 days of antibiotic treatment the patient's fever disappeared and his condition gradually improved. His temperature remained normal and the hemoglobin increased slowly. Antibiotic treatment was continued for 21 days. The patient was discharged on verapamil and disopyramide. Twenty months after discharge his physical condition remained good and he had no signs of congestive heart failure or of additional valvular lesion.

Discussion

Hypertrophic cardiomyopathy (idiopathic hypertrophic subaortic stenosis) is a well-recognized clinical entity, but bacterial endocarditis is infrequently reported as a complication. In hypertrophic cardiomyopathy the obstruction to the left ventricular outflow tract is accompanied by an abnormal systolic movement of the anterior leaflet of the mitral valve toward the interventricular septum. It has been shown recently (1) that in obstructive hypertrophic cardiomyopathy there is abnormal coaptation of the mitral valve. The posterior leaflet coapts with the mid portion of the anterior leaflet, leaving the distal residual anterior leaflet in the left ventricle during systole. A sharp angulation in this distal leaflet in mid systole toward the septum represents the systolic anterior motion. As expected, the repeated trauma upon the anterior mitral leaflet by its abutting action against the septal prominence causes endothelial lesions.

These contact lesions—in the form of mural plaques on the endocardium of the left ventricular outflow tract and on the mitral leaflets, particularly the anterior—were found in 75% of patients with hypertrophic cardiomyopathy (2). Although infection may develop on a normal valve, endocarditis is more likely to develop on previously damaged leaflets. Thus hemodynamic and anatomic observations predict that in patients with hypertrophic cardiomyopathy the mitral valve will be more susceptible to infection (2–4). A relatively small number of cases of infective endocarditis have been described in patients with hypertrophic cardiomyopathy (Table). Frank and Braunwald (5) reported three documented and three suspected cases of infective endocarditis in a group of 126 patients. Four additional large series described 15 documented (4, 6, 7) and 5 suspected, but not documented, cases of infective endocarditis (8–10). Other small series and sporadic cases have also been reported (3, 11–27).

In Braunwald's *Heart Disease,* one chapter (28) reports the incidence of infective endocarditis in hypertrophic cardiomyopathy to be 5%–9%; another chapter (29) reports an incidence of 2%.

The case reported on here is the first well-documented case of infective endocarditis among 52 patients with hypertrophic obstructive cardiomyopathy followed by our cardiology service during the eight years up to 1983. An additional patient was thought to have infective endocarditis, but no proof was available. Adding our case to the cases in the literature of the 21 years from 1961 to 1982 yields a total of 39 well-documented cases of infective endocarditis in 502 patients with hypertrophic cardiomyopathy. Another 10 cases were suspected but not definitely proven. We can summarize that the incidence of infective endocarditis in patients with hypertrophic cardiomyopathy in all large series is between 2% and 5%.

Site of Infection. The most common site for infective endocarditis in patients with hypertrophic cardiomyopathy is disputed. Frank and Braunwald (5) suggest that the aortic valve is the most common site, due to a jet lesion and abnormal valve motion. However, a high-velocity jet would be a feature only in patients with a large intraventricular gradient. Others (3, 19, 21, 25) suggest that although endocarditis may develop on a previously anatomically normal aortic valve, it is more likely to develop on the damaged endothelium of the mitral valve. Additional arguments in favor of this point of view are that most (if not all) patients with obstructive hypertrophic cardiomyopathy have mitral regurgitation (4) and most of them have thickening of the mitral leaflet (2).

We found 25 patients with reported infective endocarditis complicating hypertrophic cardiomyopathy accompanied by clinical and/or pathological findings describing the site of the endocarditic process (Table). The infection involved the aortic valve in 9 patients (5, 6, 14, 16–19, 27) and the mitral valve in 8 patients (4, 7, 23, 24). A combined mitral and aortic lesion was found in 7 patients (3, 9, 11, 25, 26). One of the 7 also had rupture of the mitral chordae tendinae (3), and in three patients the endocarditic process was localized at the endocardial surface of the hypertrophied septal prominence of the left ventricular outflow tact (6, 25). In one case endocarditis involved only the ventricular outflow tract (20). In the vast majority of cases in which infective endocarditis complicated hypertrophic cases in cardiomyopathy, various grades of mitral regurgitation and rest intraventricular gradient occurred. Of 28 patients in which intraventricular gradient was measured, 25 had a gradient more than 50 mmHg (Table).

Thus in the recorded cases the aortic valve is the most common site of infection. In addition, cases of hypertrophic cardiomyopathy with aortic insufficiency of unknown etiology were reported (5, 30). It is possible that aortic insufficiency associated with hypertrophic cardiomyopathy represents a healed infective endocarditis of the aortic valve.

Type of Bacteria. Of the 32 cases with positive blood cultures, 23 were caused by *Streptococcus* (13 cases of *S. viridans*), 7 by *Staphylococcus,* and 1 by *Corynobacterium* and *Listeria* (Table). One patient had two episodes of infective endocarditis (Case No. 13, Table).

Precipitating Causes. On examining the factors found to precipitate the infection we found 7 cases following dental extractions, 2 following cardiac catheterization, 1 following therapeutic abortion, and 1 case of an infected peripheral infusion catheter (Table). In one case, as in our patient the origin of the infection was probably the skin. In that case *Staphylococcus epidermidis* was

TABLE

Cases of Documented Bacterial Endocarditis Complicating Hypertrophic Cardiomyopathy, 1961–1982

Author	Case no.	Age	Sex	Total no. IHHS cases	Blood culture	Site of infection	Precipitating factor	LV gradient (mmHg)	Outcome
Boiteau 1961	1	37	F	U	Strep viridans	U	dental	56	S
(11)	2	23	F		Strep viridans	MV, AV	abortion	162	DA
Linhart 1966 (13)	3	29	M	U	Strep viridans	U	dental	30	S
Nagle 1967 (14)	4	34	F	U	Staph epidermidis & corynebacterium	AV	dermatitis	52	DA
Frank 1968 (5)	5	45	M	126	Strep viridans	AV	cardiac cath	95 (mean, 3 cases)	S
	6	61	F		Strep viridans	U	U		S
	7	43	F		U	U	U		S
Epstein 1969	8	20	F	22	Strep fecalis	AV	dental	110	S
(16)	9	39	M		Corynebacterium	U	cardiac cath	140	S
Cardelia 1971 (17)	10	52	M	U	Strep viridans	AV	U	63	S
Caramanian 1971 (6) includes Soulie 1962	11	41	M	120	Strep viridans	AV	U	90	S
(12)	12	17	M		Strep sanguis	AV	U	80	D
Acar 1968 (15)	13	33	M		Strep D (hemolyticus) & strep fecalis	MV, AV	dental	75	D
	14	30	F		Strep viridans	U	dental	50	S
	15	49	M		Strep H (hemolyticus)	AV	U	U	S
	16	41	F		Staph albus	MV, AV, LV	infusion cath	70	DA
Griffin 1972 (18)	17	36	M	U	Staph aureus	AV	U	U	S
Felix 1973 (19)	18	67	F	U	Strep viridans	AV	U	U	D
Hardarson	19	42	M	119	U	MV	dental	127	DA
1973	20	52	F		Strep pneumoniae	U	U	63	D
(9)*	21	59	F		Staph albus	U	U	0	S
Chretien 1973 (20)	22	66	F		Staph aureus	LV	U	U	DA
Wang 1975 (3)	23	43	F	26	Strep fecalis	MV, AV	U	U	DA
Pintor 1976 (21)	24	44	M	22	Strep viridans	U	dental	116	S
Robbins 1977 (22)	25	60	F	U	Strep mutans	U	U	U	S
Huret 1977 (23)	26	33	M	U	Staph aureus	MV	U	50	S
Pitcher 1978 (24)	27	53	M	U	Listeria monocytogenes	MV	U	U	S
LeJemtel 1979	28	58	F	U	Strep pneumoniae	MV, AV, LV	U	U	DA
(25)	29	66	F		Strep D	MV, AV, LV	U	U	D
Greenland 1979 (26)	30	57	M	5	Staph aureus	MV, AV	U	105	DA
Chagnac 1982	31	45	M	U	Strep viridans	AV	U	90	S
(27)	32	40	M		Strep viridans	U	U	U	S
	33	63	F		Strep fecalis	U	U	U	S
Kishel 1982 (7)	34–38	12–71	M (all)	U	U	MV (all)	U	45–135 (mean = 88)	2D 3S
Present case	39	57	M	52	Strep viridans	U	dermatitis	125	S

Abbreviations: IHSS, idiopathic hypertrophic subaortic stenosis; U, unknown; MV, mitral valve; AV, aortic valve; LV, left ventricular outflow; dental, dental extraction; S, survived; D, died; DA, died, autopsy.

* Described in detail first by Vecht and Oakley (4), mentioned by Swan et al (6).

isolated from blood culture, after the patient received corticotropin for poison ivy dermatitis (14).

Mortality Rate. The prognosis of patients with hypertrophic cardiomyopathy complicated by infective endocarditis might be worse than in patients with infective endocarditis in general. Of the 39 patients with infective endocarditis complicating hypertrophic cardiomyopathy, 14 in Table died in the hospital, a mortality rate of 39%—higher than the rate of 34% for infective endocarditis in general (31). Another review reported a mortality rate of 4 of 18 patients (22%) with bacterial endocarditis complicating hypertrophic cardiomyopathy (3).

Complications. Patients with hypertrophic cardiomyopathy suffer from arrhythmias which can terminate fatally. Ambulatory electrocardiographic monitoring showed that 50% had multiform or paired ventricular extrasystoles or ventricular tachycardia (26% had ventricular tachycardia) and that 46% had supraventricular tachycardia, including paroxysmal atrial fibrillation (32). It is clear that antiarrhythmic treatment is needed in these patients. In our patient, amiodarone was used to treat and prevent recurrence of ventricular extrasystoles and paroxysmal atrial fibrillation.

Among the known dermatologic complications of amiodarone, cutaneous photosensitivity was described in 3%–10% of patients (33); lesions resolved after stopping the drug. Rarely, photosensitivity may be followed by a blue-gray discoloration of the face (34, 35) and back of the hands resembling argyrosis (our unpublished data). A vasculitic skin reaction with multiple bullous lesions, typical of drug reaction, appeared in our patient, a complication which to the best of our knowledge has not yet been described with amiodarone. We believe that an infected skin lesion was the portal entry for the bacteria, which eventually caused the endocarditis.

To summarize: review of the 50 cases, 39 documented (one patient with recurrent episode) and 10 not definitely proved, among more than 500 patients with hypertrophic cardiomyopathy, reveals an incidence of this severe complication of 2%–5%, and a hospital mortality rate of 40%. In the majority of cases, mitral regurgitation and severe intraventricular gradient were observed. Infective endocarditis can involve the aortic or mitral valve, or both, chordae tendineae or the subaortic endocardium. The commonest recognized etiologic factor is *Streptococcus viridans*.

From these data it is clear that prophylaxis of bacterial endocarditis in patients with hypertrophic obstructive cardiomyopathy is mandatory.

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Gastroenterology Notes

David B. Sachar, M.D., Editor

This new column, Gastroenterology Notes, will describe the practical applications of current technologies in gastroenterology. The first article, in this issue, by Dr. Lawrence B. Cohen, director of the Gastrointestinal Motility Unit, reviews the clinical applications of gastrointestinal motility testing. Subsequent columns will describe new drugs for digestive diseases (Dr. Gerald E. Friedman) and diagnostic and therapeutic applications of gastrointestinal endoscopy (Dr. Peter H. Rubin). The aim of these articles is to be practical, readable, and informative. Larry Cohen gets us off to a good start.—DBS

Clinical Applications of Gastrointestinal Motility Tests

Lawrence B. Cohen, M.D.

With recent advances in technology, and the ability to directly record motor responses in the esophagus and colon, our understanding of motility disorders of these two organs has greatly expanded. Despite this progress, however, clinical application of these modalities in the diagnosis of gastrointestinal motility disorders has been limited. Currently, the gastrointestinal motility unit can provide the clinician with information useful in the evaluation of several disorders of motor function. These findings can have both diagnostic and therapeutic significance.

In this review I attempt to outline a basic understanding of the disorders of esophageal and colonic motility and discuss, first, a systematic approach to the evaluation of the clinical problems and, second, specific indications for use of the gastrointestinal motility unit.

Disorders of Esophageal Motility

The clinical conditions affecting esophageal motility can be divided into primary disorders, which involve only the esophagus, and secondary disorders, in which the esophagus is involved as part of a more generalized process (Table 1). Primary disorders of esophageal motility are characterized by the typical esophageal symptoms of chest pain and/or dysphagia, and esophageal manometry is particularly helpful in confirming the diagnosis. Disorders of esophageal motility due to systemic diseases are less often symptomatic, but manometric studies can provide an important tool in the diagnosis of these entities as well.

Primary Disorders. *Achalasia* is a motor abnormality affecting the smooth-muscle portion of the lower esophagus, in which peristalsis is diminished or absent, and the lower esophageal sphincter fails to adequately relax during swallowing. Dysphagia is the most frequent symptom, occurring in nearly all patients. Manometric evaluation is confirmatory in most patients when the diagnosis is suggested by radiography and upper endoscopy.

Diffuse esophageal spasm frequently produces symptoms of both chest pain and dysphagia due to chaotic, disorganized bursts of contractile muscular activity in the smooth-muscle portion of the esophagus. Between episodes of spasm, contractile activity may be normal, and manometric testing may not be diagnostic. The use of various provocative agents during manometry, such as edrophonium and bethanecol (1–3), has permitted greater diagnostic accuracy.

Achalasia and diffuse esophageal spasm may not be distinct diseases, but two extremes of the

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TABLE 1
Esophageal Motility Disorders

- Primary disorders
  - Achalasia
  - Diffuse esophageal spasm
  - Nutcracker esophagus
  - Nonspecific dysfunction
    - Hypertensive lower esophageal sphincter
    - Diminished amplitude of esophageal peristalsis
    - Vigorous achalasia
- Secondary disorders
  - Scleroderma
  - Other connective tissue disorders
  - Diabetes mellitus
  - Presbyesophagus
  - Chronic idiopathic intestinal pseudoobstruction
  - Chagas disease

Adapted from Benjamin SB, Richter JE, Cordova CM et al. Gastroenterology 1983;84:893–901.

same basic process (4). Transition from diffuse spasm to achalasia in a single patient has been well documented (5, 6).

Vigorous achalasia is a variant of achalasia in which high-amplitude contractions occur in the body of the esophagus in association with achalasia (7). This condition may represent a transitional state between diffuse esophageal spasm and achalasia.

Many patients with symptoms of dysphagia or chest pain have a less distinct manometric pattern. Isolated abnormalities of the lower esophageal sphincter or esophageal body can occur. The lower esophageal sphincter may be hypertensive, but still relax completely during deglutition. This abnormality can occur alone or in conjunction with diffuse esophageal spasm (8). High-amplitude peristaltic contractions of the esophageal body, called the "nutcracker esophagus," may explain symptoms of chest pain in some patients with these motility findings (9).

Gastroesophageal reflux of acid may induce disorders of esophageal motility which mimic diffuse spasm. When acid reflux is clinically suspected, patients should be treated for this condition before receiving a diagnosis of primary motor disorder of the esophagus. However, one should also remember that esophageal acid perfusion in patients with coronary artery disease can result in chest pain and electrocardiographic changes indicating myocardial ischemia (10).

Secondary Disorders. Esophageal motor function can be altered in several systemic diseases.

Scleroderma involves the esophagus in up to 75% of patients (11). This disease produces atrophy of the smooth-muscle portion of the esophagus, resulting in diminished amplitude of contraction in the distal esophageal body and a reduction of lower esophageal sphincter pressure. As a consequence, increased reflux of acid and delayed acid clearance may produce esophagitis and stricture formation. Esophageal manometric evaluation is useful in both the preclinical and clinical stages of the disease, and may document systemic disease long before esophageal involvement is clinically evident.

Diabetes mellitus is also commonly associated with a disturbance of esophageal motility. Up to 80% of diabetics with autonomic neuropathy will have abnormal esophageal motility (12), resembling the changes seen after vagotomy. Despite the frequency of these abnormalities, most patients remain asymptomatic.

Chronic idiopathic intestinal pseudo-obstruction, like diabetes, frequently produces detectable changes in esophageal manometry (13). Although most patients are asymptomatic, esophageal manometry provides a useful diagnostic tool in confirming this difficult diagnosis.

Approach to Esophageal Dysfunction

The major symptoms of esophageal disease include dysphagia, chest pain, and heartburn.

Dysphagia. In approaching patients with dysphagia, the clinician should first exclude possible mechanical causes. The barium esophagram and flexible esophagoscopy are both useful to assess the esophagus. In the absence of mechanical obstruction, radiographic features suggestive of a motor disorder may or may not be present. During endoscopy, particular attention should be paid to the gastric cardia in order to exclude a gastric neoplasm invading the lower esophageal sphincter and producing "pseudo-achalasia" (14).

If these tests fail to demonstrate a mechanical factor accounting for the patient's symptoms, esophageal manometry should be performed. Manometry will be most useful in diagnosing achalasia, scleroderma, diffuse esophageal spasm, and the nonspecific motor disorders. It will occasionally confirm the diagnosis of chronic idiopathic intestinal pseudoobstruction, or demonstrate abnormal esophageal peristalsis in the diabetic with symptomatic esophageal dysfunction.

Chest Pain. Episodic chest pain or pressure requires careful evaluation by the clinician to exclude coronary artery disease. Once coronary disease has been ruled out, an esophageal etiology should be considered. A systematic evaluation

TABLE 2
Disorders of Colonic Motility

- Irritable bowel syndrome
- Hirschsprung's disease
- Chronic idiopathic intestinal pseudoobstruction
  - Myopathic
  - Neuropathic
- Idiopathic constipation
- Cathartic colon
- Diabetes mellitus
- Myxedema
- Scleroderma
- Chagas disease
- Familial autonomic dysautonomia
- Parkinson's disease
- Amyloid
- Pharmacologic
  - Phenothiazines
  - Tricyclic antidepressants
  - Anti-Parkinsonian medications
  - Ganglionic blockers
  - Clonidine

should begin with a barium esophagram. Radiographic examination is most helpful in demonstrating neoplastic lesions, esophageal ulceration, and gastroesophageal reflux with esophagitis. The esophagram is less often reliable for disorders of esophageal motility, but may be positive in up to 54% of patients (15).

A complete manometric evaluation in patients with chest pain includes baseline manometric study, and if the baseline study is normal, provocative testing is performed with cholinergic agents to reproduce the patient's symptoms. If both baseline and provocative tests are negative, an acid perfusion (Bernstein) test is necessary to exclude acid reflux as the etiology of the patient's symptoms. Twenty-four-hour ambulatory monitoring of esophageal pH may prove to be helpful in the evaluation of symptomatic gastroesophageal reflux in patients with unexplained chest pain (16), but additional studies are needed before the utility of this test is proven. Unfortunately, many patients remain undiagnosed despite extensive testing (17). Our technical abilities are inadequate to establish a definitive diagnosis in all patients.

Heartburn. Esophageal manometry has little role in the diagnosis or treatment of heartburn (18). The symptom complex is usually established from the patient's history, and no further tests are necessary. If symptoms continue with routine measures, evaluation with an upper gastrointestinal series or esophagogastroduodenoscopy may be helpful to confirm the diagnosis and document the need for strict medical management. Further confirmation can be obtained using the gastroesophageal scintiscan.

The use of esophageal manometry should be reserved for patients in whom a surgical antireflux procedure is planned. In patients with severe esophagitis, peristalsis can be markedly diminished or absent, and fundoplication may result in postoperative dysphagia. To avoid such complications, patients with esophagitis and weak peristaltic contractions undergoing surgery should probably have a "loose" fundoplication.

Disorders of Colonic Motility

Irritable Bowel Syndrome. Irritable bowel syndrome may involve any part of the gastrointestinal tract; altered motility of the esophagus, stomach, and small intestine, as well as of the colon, have all been described in this syndrome (19–21). Symptoms include abdominal pain, distention, and an alteration of bowel habits (diarrhea or constipation, or both). The complaints are intermittent and may be exacerbated by emotional stress. Diagnosis of the syndrome is based on the clinical picture, with particular emphasis on the history, although sigmoidoscopy and radiographic studies may sometimes be necessary to exclude other disorders.

The precise nature of the motility disorder in this syndrome has not been firmly established. Both increased and decreased sigmoid motor activity have been described (22, 23). Although several studies of patients with the disorder have identified specific patterns of myoelectric and motor activity (21), these findings are neither specific nor readily reproducible and hence are not clinically useful in confirming the diagnosis (24).

Hirschsprung's Disease. Congenital megacolon is characterized by the absence of ganglion cells in the distal segment of colon. The aganglionic segment usually extends proximally from the anus, involving variable lengths of colon. In most patients, the transition to normal ganglionic bowel occurs in the rectum or distal sigmoid. The disease usually begins with constipation and abdominal distention in infants before age 2, but cases have been reported in patients up to 67 years of age.

The diagnosis should be suspected on barium enema, which demonstrates a narrow distal segment with dilated colon above. Anorectal manometry is diagnostic; instead of the normal internal sphincteric reflex which results in relaxation, virtually 100% of patients with Hirschsprung's disease will demonstrate a paradoxic contraction of the sphincter during transient balloon distention of the rectum (25). This simple, rapid test can be performed in infants and adults and is the best screening test for the diagnosis of Hirschsprung's disease. A deep rectal biopsy demonstrating absence of ganglia is helpful in certain cases when a surgical procedure is contemplated.

Chronic Idiopathic Intestinal Pseudo-Obstruction. Most cases of chronic idiopathic intestinal pseudo-obstruction, a diffuse disorder of intestinal motility (26, 27), begin in childhood, although some may go undiagnosed for several decades. Patients usually experience life-long constipation, although secondary diarrhea may develop due to intestinal hypomotility, stasis, and bacterial overgrowth. Upper gastrointestinal symptoms of esophageal or gastric etiology may be present. The disorder is usually an inherited one.

Two forms of the disorder are found: myopathic, involving intestinal smooth muscle diffusely; and neuropathic, for which involvement of the autonomic nervous system is believed responsible. In the neuropathic group of patients, other disturbances of autonomic function, including orthostatic hypotension and sluggish papillary reflexes, may be present. The rectosphincteric inhibitory reflex is preserved in these patients, but colonic motor response to feeding is blunted, providing a useful clinical test (28). The diagnosis should be suspected when dysfunctions of several areas of the gastrointestinal tract are demonstrated. Treatment is medical, and surgery should be avoided.

Application of Manometric Studies

The clinical gastrointestinal motility unit can provide both diagnostic and therapeutic help in the management of patients with disorders of colonic motility. In patients with constipation of unknown etiology, study of the rectosphincteric reflex and pressure profile of the sphincter provide useful clinical data (28). In such patients, the diagnosis of Hirschsprung's disease, when suspected, can be established or ruled out by these evaluations. Alternatively, disorders of smooth muscle or of the autonomic nervous system can be suggested by finding reduced basal internal sphincter pressure and loss of the normal inhibitory reflex. An occasional patient with severe constipation but with normal gastrointestinal transit will turn out to have outlet obstruction at the anal sphincter (29). Measurement of the sphincter profile reveals high basal pressures but normal relaxation. A simple anorectal myotomy may be therapeutically helpful in these patients.

The motility laboratory can also serve a therapeutic purpose for patients with fecal incontinence (30, 31). The various etiologies of this problem include previous rectal surgery or trauma, diabetes mellitus, and spina bifida. Manometric studies demonstrate decreased basal and maximum sphincter pressures. By receiving visual cues from the direct-writing display recorder, patients with fecal incontinence can be taught sphincter-strengthening exercises to increase tone of the external sphincter. In patients in whom sensation to rectal distention is reduced, enhanced sensory awareness can also be learned (32). This biofeedback technique is relatively simple, can usually be learned at one visit, and provides help to patients with this socially embarrassing disorder.

Conclusion

Manometric evaluation of disorders of gastrointestinal motility has its greatest potential value in patients with disturbances of esophageal function. Esophageal manometry is particularly useful in the study of patients with symptoms of dysphagia or chest pain when radiographic or endoscopic tests are normal. In many such patients, a motor disorder of the esophagus can be demonstrated; the use of pharmacologic agents for provocation during manometry has enhanced our ability to recognize these disorders.

Measurements of colonic motility and anorectal sphincter function have also provided an important, albeit more limited, diagnostic tool. Studies of sphincteric function are helpful in patients with disabling constipation when a surgically remedial cause is sought. At present, colonic motility tracings are not yet clinically useful in the diagnosis or management of irritable bowel syndrome, but further investigation may result in improved methods of study for this widely prevalent disease.

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An Unusual Cause of Tetany: Surreptitious Use of Furosemide

HORACIO KAUFMANN, M.D., FERNANDO ELIJOVICH, M.D., AND MELVIN D. YAHR, M.D.

Patients with electrolyte imbalance are a challenging diagnostic problem. Though many causes exist, one relatively common cause is long-term use of diuretics, which may not be readily evident, especially in emotionally disturbed individuals. Such patients tend to conceal their drug usage (1) and diagnosis can only be made after extensive investigative studies that exclude all other possible causative factors.

We recently encountered an unusual case in which surreptitious use of a diuretic induced electrolyte abnormalities which led to periodic episodes of tetany. Blood chemistries revealed hypokalemic metabolic alkalosis, the characteristic manifestation of diuretic abuse, and severe hypocalcemia and hypomagnesemia.

Studies of electrolyte balance and the response of the renin-angiotensin system to sodium restriction and sodium loading provided strong evidence supporting diuretic abuse. Though the patient had previously denied the use of diuretics, when these findings were presented to her, she finally admitted long-term intake of furosemide.

Case Report. A 43-year-old white woman had tetanic episodes, approximately twice a month, for two years. Each episode consisted of a typical carpopedal spasm preceded by perioral paresthesiae. Her medical history was noncontributory except for a daily intake of about four ounces of whiskey. Repeated physical examinations had disclosed Trousseau's and Chvostek's signs as the only detectable abnormalities. Her blood pressure was consistently within normal limits. Laboratory data showed persistent hypokalemic metabolic alkalosis and hypocalcemia. Oral replacement of potassium and calcium salts had not improved the clinical picture. Acute tetanic attacks occasionally responded to CO_2 rebreathing or intravenous calcium gluconate. No clearcut diagnosis had been established for her metabolic abnormalities. The patient denied self-induced or spontaneous vomiting as well as intake of cathartics or diuretics. She only reported a short period of furosemide treatment, long before the first attack of tetany.

On admission to The Mount Sinai Hospital, her blood pressure was 120/80 mmHg. The only abnormal physical findings were in the neuromuscular system. Trousseau's and Chvostek's signs were easily elicitable. Bilateral weakness of the hip extension (4/5 MCR scale) and a fine distal tremor of the hands were also noted. Deep tendon reflexes were symmetrically brisk but plantar responses were normal.

Hematologic laboratory data included white blood cell count $7.5 \times 10^3/mm^3$, platelet count 323,000/mm3, Hb 10.7 gr%, Hct 32.7%, MCV 93 $\mu 3$, serum iron 75 mcg/dl (45-200), serum folate 11 ng/ml, (5-12), serum B_{12} 302 pg/ml (300-1200) and haptoglobin 180 mg%. Direct and indirect Coombs test and serial stool guaiacs were negative. Bone marrow aspirate and biopsy showed normal erythropoiesis, myelopoiesis, and megacaryocytopoiesis and normal iron stores.

Blood chemistries disclosed serum sodium of 146 mEq/1, chloride 101 mEq/1, CO_2 28 mEq/1, calcium 7.9 mg%, phosphorus 2.2 mg%, magnesium 1.13 mEq/l, BUN 28 mg%, creatinine 0.8 mg%, uric acid 10 mg%, total protein 7.1 g%, albumin 4.1 g%, pO_2 94 mmHg, pCO_2 35 mmHg, pH 7.57, HCO_3 29 mEq/l. Plasma immunoreactive PTH (C-terminal) was 105 μlEq/ml. Calculated tubular reabsorption of phosphorus was 81%. Urine calcium excretion was 80 mg/24 hr.

X-rays of the skull, femur, and humerus did not

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show evidence of demineralization. EKG showed a normal sinus rhythm and a prolonged QT interval consistent with her electrolyte imbalance.

Intestinal malabsorption was excluded by normal Schilling's and d-xylose tests, normal serum level of B-carotene, and normal contents of fat in a 72-hr stool sample. Upper gastrointestinal series, small-bowel follow-through, and barium enema were normal.

Electromyographic studies showed pseudomyotonia and increased irritability in the distal muscles. Ischemic testing of the left upper extremity with a blood pressure cuff demonstrated exacerbation of these phenomena.

Plasma renin activity (PRA) and plasma aldosterone were initially measured in the upright posture while the patient was on her usual diet. Immediately thereafter, a diet containing 10 mEq/day of sodium and 100 mEq/day of potassium was given for four days. The morning of the fifth day, an intravenous sodium load (290 mEq/2 hrs) was administered. PRA and aldosterone responses to sodium restriction and sodium load were assessed at the end of each period after overnight recumbency and 2 hours of upright posture. Daily measurements of serum and urinary electrolytes were carried out throughout the study.

Serum sodium did not change significantly over the three dietary periods. Sodium balance ($U_{Na}V < 10$ mEq/day) was achieved after three days on the low sodium diet. Before dietary manipulations, urine excretion of potassium was inappropriately high for the degree of hypokalemia (Fig. 1). In contrast, over the rest of the study, urinary potassium amounted to only 20%–30% of oral intake (middle panel). This led to a positive cumulative balance of 384 mEq of potassium over 5 days (bottom panel) and to a slowly progressive correction of serum potassium (top panel).

Before dietary manipulations, upright PRA was increased approximately fivefold (Table). After sodium restriction, PRA was paradoxically reduced to half its previous levels. Physiologic stimulation of renin release by upright posture was well preserved during sodium restriction. Although the acute sodium load was not enough to suppress PRA further, the response to upright posture was blunted after this maneuver. Baseline plasma aldosterone levels were 33 ng/dl. Changes in plasma aldosterone by sodium restriction and sodium load were entirely consistent with PRA values in all phases of the study.

During the course of the hospitalization, serum levels of calcium, magnesium, phosphorus, CO_2, uric acid, cholesterol, and plasma parathyroid hormone returned to normal values. Muscle strength improved considerably and no further tetanic attacks occurred. Clinical and electromyographic signs of pseudomyotonia disappeared.

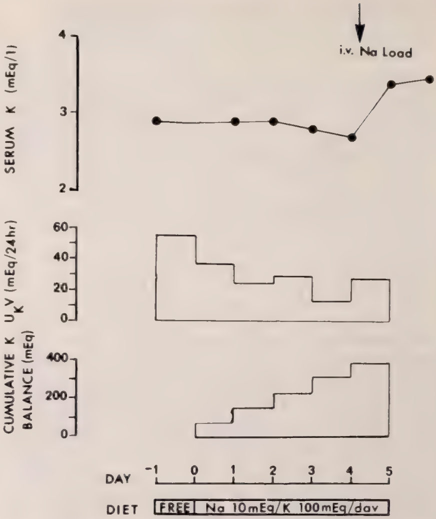

Fig. 1. Effects of dietary sodium restriction and intravenous sodium loading on serum and urine potassium and cumulative potassium balance.

Confronted with the strong evidence provided by the laboratory data, the patient ultimately admitted to surreptitious intake of furosemide for prevention of "fluid retention." She was discharged from the hospital after being advised about the risks of further diuretic intake and the need for psychiatric treatment.

Discussion. Tetany, an unusual manifestation of diuretic abuse (2), was the predominant clinical feature in our patient. Hypocalcemia and hypomagnesemia were associated with the characteristic hypokalemia which is observed in this entity.

TABLE

Changes in Plasma Renin Activity (ng A_I/ml/hr) in Relationship to Sodium Intake

Body posture	Unrestricted sodium	Restricted sodium	Sodium load
Supine	—	7.8	7.8
Upright	26	13	6.5

Other causes of hypokalemia were considered before the diagnosis was established. Primary hyperaldosteronism, extremely unlikely in normotensive patients (3), was definitely excluded by the marked elevation of plasma renin activity. Renin stimulation and elevation of plasma aldosterone excluded intake of licorice.

The differential diagnosis between Bartter's syndrome and surreptitious intake of diuretics or other cathartics or self-induced vomiting is often a clinical dilemma. Bartter's syndrome may be documented by detection of its characteristic defect in platelet aggregation (4). However, this laboratory technique is not widely available. Techniques for the detection of certain diuretics in the urine have been developed (5). However, final proof for abuse of these drugs is not readily obtained unless patients admit to their intake.

In our patient, the major piece of evidence leading to the suspicion of self-administration of medications was the paradoxical reduction of a markedly increased baseline plasma renin activity (PRA) by one of its physiologic stimuli, sodium restriction. This finding did not represent an intrinsic abnormality of the renin angiotensin system. The physiologic increase in PRA produced by upright posture and the appropriate blunting of this response by sodium load demonstrated normal regulation of renin release.

The data suggested that potent stimulation of PRA had taken place prior to admission. We thought that after hospitalization, when the putative stimulus for renin release had been withdrawn, the resulting decrease in PRA overcame the normal stimulatory effect of a low sodium diet. Contributory evidence for this hypothesis was the rapid achievement of sodium balance and the retention of potassium over the period of controlled dietary conditions. These suggested prior dehydration and electrolyte loss.

A diuretic seemed the most likely culprit. Urine potassium excretion the day of admission was inappropriately high for the hypokalemic state, suggesting drug-induced kaliuresis. Hyperuricemia, elevated serum bicarbonate, and hypercholesterolemia (biochemical abnormalities that accompany diuretic use) not only were present but disappeared during the period of hospitalization without specific treatment. A definitive diagnosis was made when the patient admitted to long-term oral intake of furosemide.

Furosemide increases urinary excretion of calcium and magnesium by direct inhibition of tubular reabsorption of both cations at the ascending loop of Henle (6). However, hypocalcemia with tetany has rarely been described in relationship to use or abuse of this diuretic (2). Maintenance of normal serum calcium by stimulation of PTH is the most likely explanation for the prevention of these abnormalities.

Other causes of hypocalcemia were excluded in our patient. Primary hypoparathyroidism was ruled out by the increase in immunoreactive PTH and hypophosphatemia. Renal unresponsiveness to the action of PTH (a form of pseudohypoparathyroidism) was excluded by the decreased renal tubular reabsorption of phosphorus. Furthermore, the physical findings characteristic of this entity were not present (7). Intestinal malabsorption as a cause for secondary hyperparathyroidism was ruled out by multiple laboratory and radiologic procedures. Osteomalacia seemed an unlikely possibility in view of the absence of gross abnormalities in the x-rays of long bones.

Furosemide-induced hypercalciuria could eventually lead to hypocalcemia and tetany if the compensating skeletal reabsorption of calcium became impaired. Hypomagnesemia, another consequence of furosemide administration, is known to inhibit the skeletal response to PTH (8, 9). However, either the degree of hypomagnesemia produced by furosemide is not enough for the development of hypocalcemia and tetany, or tetany is prevented by the simultaneous depletion of potassium (10, 11).

At least three other causes for magnesium depletion were present in our patient. Oral calcium supplements decrease intestinal absorption of magnesium by competing for the transport mechanism shared by these two cations (12). Chronic intake of alcoholic beverages produces hypomagnesemia through complex mechanisms not yet well understood (13). Aldosterone, which was markedly elevated in our patient, has been shown to increase the urinary clearance of magnesium (14). Whether the sum of these circumstances led to a more severe degree of magnesium depletion than that observed due to furosemide alone cannot be ascertained from our studies. Severe magnesium depletion may not only facilitate tetany through impairment of the reabsorptive action of PTH on bones, but may also increase muscle excitability through release of acetylcholine from nerve endings (15).

Whatever the mechanisms involved, the reversal of all the abnormalities of calcium metabolism after discontinuation of furosemide constituted definitive confirmation that tetany had been caused by this diuretic agent.

In summary: this case report demonstrates that despite a complex and unusual mode of presentation. detailed studies of electrolyte balance and the renin-angiotensin system may provide strong evidence favoring one of the multiple possible diagnoses for hypokalemia. Confronting patients with the results may identify them as members of a subset of emotionally distressed patients prone to admit surreptitious intake of a drug. This can only facilitate their management and prognosis.

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Ophthalmologic Notes *Keith M. Zinn, M.D., Editor*

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Partial Avulsion of the Optic Nerve Head Secondary to Local Trauma: Case Report

KEITH M. ZINN, M.D., AND ELAINE H. KIRBAN, M.D.

Avulsion of the optic nerve from the globe occurs as a result of trauma either to the globe itself or to the orbit, or to both (1–3). In some instances, extension of bony fragments or direct penetration by foreign bodies is responsible for the avulsion process. In other cases, orbital shearing forces damage the pial tissue covering the optic nerve and lead to avulsion of the optic nerve head. In still other cases trauma can create an explosive rise in the intraocular pressure of the globe and saw the optic nerve head off at the lamina cribrosa or at the scleral foramen and propel the nerve head into its dural sheath in much the same way that a cork exits a champagne bottle.

A number of case reports in the literature have described partial and total avulsions of the optic nerve head (4–9), and several authors have described the fluorescein angiographic findings in these cases (3, 10–11). In the case reported here, the patient, while playing basketball, was poked in the eye with a finger by another player. The mechanism for the avulsion of the optic nerve head is believed to be the orbital forces transmitted directly to the optic nerve itself.

Case Report

An 18-year-old male student, in good general health most of his life, was playing basketball on July 9, 1983 when he was jabbed in the right eye with a finger by another player and immediately noted marked visual loss in the right eye. That day an ophthalmologist noted a vitreous hemorrhage in the right eye, and placed the patient on high doses of oral prednisone (80 to 100 mg a day). No significant improvement of vision occurred, and after several weeks the systemic steroids were tapered. The patient had also been placed on topical steroids and mydriatic agents to the right eye.

I saw the patient for the first time twelve days after the injury and the ocular findings were as follows:

Visual acuity, without any correction, was hand motion at 1 foot in the right eye and 20/30 in the left eye. Manifest refraction could not improve the visual acuity in either eye.

Extraocular motility studies revealed a full range of motion of either globe in all standard fields of gaze and the eyes were straight to the primary position of gaze.

Cranial nerve function II, III, IV, ophthalmic division of V, VI, ophthalmic division of V, VI, and VII were grossly intact bilaterally except for the marked visual reduction in the right eye at the hand motion level.

The lids, ocular adnexae, and lacrimal gland apparatus were essentially within normal limits bilaterally. The palpebral and bulbar conjunctiva, cornea, and sclera were also within normal limits bilaterally, except for a bulbar conjunctival hemorrhage located between the 3 o'clock meridian clockwise through the 4 o'clock meridian in the perilimbal region of the right eye.

The intraocular pressures were 19 mm Hg in the right eye and 17 mm Hg in the left eye by applanation tonometry.

Slit-lamp examination of the anterior chambers revealed them to be clear, of moderate depth, with about a grade IV open anterior chamber angle for 360 degrees in both eyes. Contact lens gonioscopy in each eye failed to reveal any evidence of an angle recession. The irides were blue bilaterally. The right pupil was dilated at approximately 6 mm in its transverse diameter and on distant target fixation did not react to light or accommodative targets due to the previously in-

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stilled mydriatic eye drops. The left pupil was about 3 mm in transverse diameter on distant target fixation and reacted briskly to light and accommodative targets.

The lenses appeared to be grossly clear, but the posterior surface of the right lens was covered with a layer of red blood cells in several regions. The left lens was perfectly clear and unremarkable. The vitreous cavity in the right eye had numerous areas of vitreous hemorrhagic debris whereas the vitreous cavity in the left eye was clear and unremarkable.

Funduscopic examination of the right eye revealed an avulsed optic nerve head superiorly with hemorrhage in the peripapillary region (Fig. 1). The cup/disc ratio could not be estimated because of the overlying vitreous hemorrhagic debris as well as the oblique angle of the avulsed right optic nerve head. The cup/disc ratio, in the horizontal meridian, was 0.2 in the left eye. The vein:artery ratio, at the disc margin, was 4:1.5 in the right eye and 3:2 in the left eye. Details of the macular region were somewhat obscured by the overlying vitreous hemorrhage in the right eye. The left macular region was grossly within normal limits, with a good foveal reflex and normal macular pigmentation.

Peripheral indirect ophthalmoscopy with scleral depression could be carried out in a somewhat limited fashion in the right eye due to overlying and fairly dense vitreous hemorrhagic debris in the periphery of the right eye. The retina observed on ophthalmoscopy appeared to be attached in the posterior polar region of the globe. However, all details of the retinal periphery were obscured by peripheral vitreous hemorrhagic debris in the right eye.

Peripheral indirect ophthalmoscopy in the left eye revealed a meridional fold with several peripheral intraretinal tags midway between the equator and the ora serrata region at the 9:30 and 9:45 o'clock meridians of the left eye. Otherwise a zone of 1+ white-with-pressure was present, extending from the equator anteriorly to the ora serrata region and running from 360 degrees in the left eye.

A fluorescein angiogram was performed with the following findings:

Kodachromes of the right disc and macular region (Fig. 1) revealed a definite avulsion of the superior portion of the right optic nerve head from the optic foramen. The retinal vessels appeared to be intact inferiorly and the vein:artery ratio, at the disc margin, was about 4:1.5 OD. There was optic pallor in the remaining portion of the right optic nerve head. Peripapillary choroidal atrophy was noted along the temporal border of the right optic nerve head. Superficial splinter hemorrhages of the retina were noted at the superonasal border of the right optic nerve head, and a possible cotton-wool spot lesion was also noted just superotemporal to the right optic nerve head. The macular region appeared to be grossly within normal limits OD.

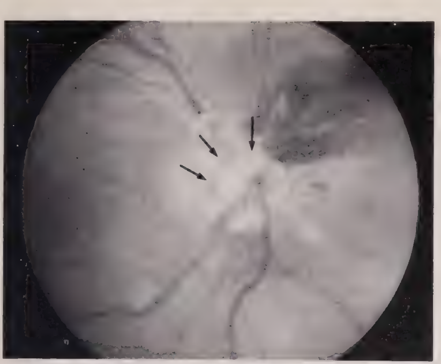
Red-free photographs of the right eye (Fig. 2) were consistent with the above description.

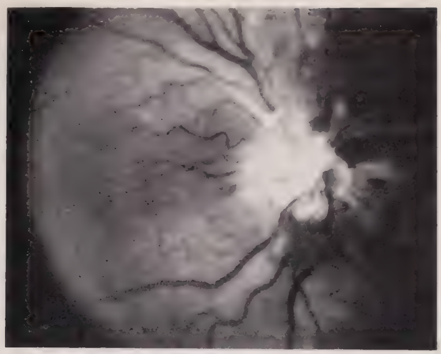
Rapid sequence fluorescein angiography of the right eye revealed (Fig. 2) relatively prompt retinal arteriolar filling at about 18 seconds after injection of fluorescein dye into a vein located in the antecubital fossa of the left upper extremity. There appeared to be a normal retinal arteriolar-venous transit time involving the retinal vessels in the inferotemporal and inferonasal quadrants, but there was a definite delay in the retinal venous filling time involving the superotemporal and superonasal retinal veins. The superficial and deep retinal hemorrhages acted as hypofluorescent lesions blocking underlying normal choroidal fluorescence. The superior portion of the optic nerve head, where the avulsion was present, appeared to have no capillary bed filling with fluorescein dye. In the late stages of the angiogram, there was some staining inferiorly of the optic nerve head and minimal staining superiorly at the edge of the optic foramen. There did not appear to be any abnormal leakage of fluorescein dye from the retinal or choroidal circulations in the right eye.

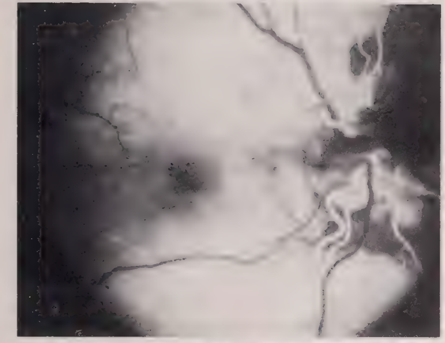
Discussion

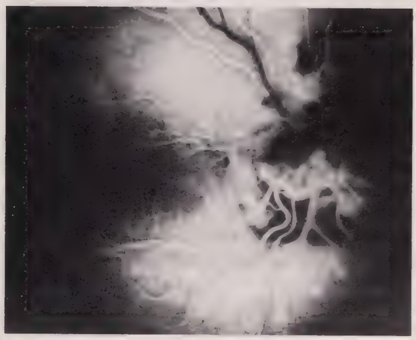
This patient sustained a vitreous hemorrhage secondary to a partial avulsion of the optic nerve head due to orbital trauma. The actual diagnosis was delayed until the vitreous hemorrhage had cleared sufficiently to view the optic nerve head. Perhaps electroretinogram and visually evoked response testing immediately after the injury could have helped establish the diagnosis earlier, before the vitreous hemorrhage had cleared.

In the case presented, the retinal vessels at the avulsion site seemed to be intact and did fill with fluorescein dye on angiography. The mechanism for the venous delay and occlusive picture was probably stretching and secondary compression of the retinal-optic disk vessels over the scleral foramen at the avulsion site, as suggested by Hart









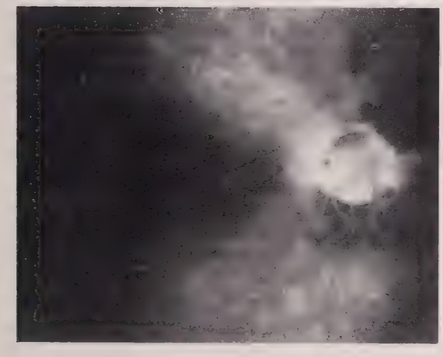


Fig. 1. Top Left Fundus photograph of right eye. Avulsion of optic nerve head superiorly (arrows); widening of veins with superficial and deep retinal hemorrhages in optic nerve and peripapillary region superiorly.

Fig. 2. Fluorescein angiogram of partially avulsed optic nerve head in right eye. **Top right** Red-free photograph. **Center left** Early retinal arterial-venous phase. Delay in retinal venous filling superiorly compared to inferiorly; superior retinal veins are wider than inferior veins. Despite loss of capillary filling on superior half of nerve head, all major branches of central retinal artery appear to be intact and filled equally with fluorescein dye. **Center right** Mid retinal arterial-venous phase. Loss of capillary filling on superior portion of optic disk; retinal venous filling time is delayed superiorly compared to inferiorly. **Left** Late phase. Normal late staining of nerve head inferiorly with fluorescein dye; only minimal staining in superior avulsed portion.

and Pilley (10). In other cases, in the literature, it has been suggested that anastamoses have developed between the peripapillary choroidal vessels and the avulsed retinal vessels (5).

The fluorescein angiogram, in this case, showed absence of capillary filling in the superior half of the optic disk central to the avulsion cleft. There was minimal staining of the superior edge of the optic foramen in the late stages of the angiogram. In some other cases, described in the literature, there has been leakage of fluorescein dye reported over the margins of the avulsion site. Hayreh (12) has used this latter observation along with other evidence to suggest that the optic nerve head does not receive a blood supply from the major retinal vessels within the margin of the disk, but probably from the choroidal circulation.

The absolute inferior altitudinal visual field cut in this case corresponds to the superior avulsion site at the optic nerve head and is testimony to the severity of the trauma. Understandably, early diagnosis and treatment with megadose steroids (13, 14) in a range greater than 1 mg per kilogram of body weight of dexamethasone sodium phosphate per day does not appear to have a beneficial influence on the visual outcome in these cases. It has been suggested (13, 14) that, in some cases of indirect trauma to the optic nerve with edema and optic nerve compression, megadose steroids do help the visual outcome. However, little can be done once the optic nerve fibers have been severed. Finally, in cases with a vitreous hemorrhage in which trauma to the orbit, to the globe, or to both has taken place, one should consider partial or complete avulsion of the optic nerve head as a diagnostic possibility.

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Radiology Notes

Jack G. Rabinowitz, M.D., Editor

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With this issue we are reintroducing "Radiologic Notes," long a well-appreciated section of this journal. As a tribute to the previous editors, Drs. Peck and Bloch, I will attempt to maintain its familiar format. "Radiology Notes" will therefore continue to consist of multiple interesting, concise reports of cases with discussions that include major radiologic points of diagnostic significance.—JGR

Case 1

Richard B. Ruchman, M.D., Rhona J. Keller, M.D., A. Sicular, M.D., and A. D. Hauser, M.D.

Case Report. This 61-year-old woman was admitted to the hospital because of rectal bleeding and melena of 3 months' duration, accompanied by intermittent fever and vomiting. She had also experienced poor appetite and loss of an unknown amount of weight. Examination revealed a nontender, irregular 8 × 10 cm right upper quadrant mass not fixed to the abdominal wall. Laboratory examination showed alkaline phosphatase 215, serum GPT 83 mg/100 ml, serum GOT 94 mg/100 ml, total protein 6 gm/100 ml, albumin 2.7 gm/100 ml, hemoglobin 9.9 gm/100, hematocrit 19.5%, white blood cell count 13,600 with 75 polymorphonuclear leukocytes.

An ultrasound examination of the abdomen on the day of admission showed a solid subhepatic mass that measured 7 × 8 × 10 cm. The gallbladder could not be identified. On barium enema examination performed the following day, the mass was noted to compress the proximal transverse colon, producing marked distortion of the mucosal folds (Fig. 1). In addition, a lucent zone with smooth contours extended outside the colon. An upper gastrointestinal contrast examination showed fistulae extending from the mass to the duodenum and colon (Fig. 2). Within the extravasated contrast, at least one and perhaps two filling defects were evident, suggesting the presence of gallstones (Fig. 2).

At surgery a huge necrotic mass was found enveloping the gallbladder and the proximal transverse colon (Fig. 3). A cholecystoduodenal fistula, cholecystocolonic fistula, paracolic abscess, and gallstones were found. This was felt to represent a primary carcinoma of the gallbladder with extrinsic involvement of the surrounding viscera. A cholecystectomy was performed with a marginal liver resection, transverse colectomy, oversewing of the duodenal fistula, colostomy, gastrostomy, and feeding jejunostomy. The patient was discharged to her home on the twentieth postoperative day.

Discussion. Carcinoma of the gallbladder is the fifth most common malignant disease of the gastrointestinal tract. One large series reported an incidence ranging from 0.2 to 1.0% (1). The number of new cases diagnosed each year has been estimated as 5,000 to 6,000 (2). Most studies have demonstrated a female predominance varying from 1.8:1 to 3:1 (3–5). It is found more commonly among the elderly; in 80% of patients, mean age is over 60 years. The etiology of gallbladder cancer is unclear; however, its association with gallstones or porcelain gallbladder is well-known.

Unfortunately, the clinical and laboratory features of gallbladder cancer are nonspecific and rarely made (1, 6, 7). The lesion is frequently discovered late, after the tumor has locally invaded unresectable structures. Aside from the few patients whose tumor is discovered accidentally during surgery, it is rare to find a patient surviving beyond 5 years (8). The prognosis has not been altered significantly by the extent of surgery or the method of treatment (9).

The plain film contributes little to the diagnosis of gallbladder cancer, aside from delineating gallstones or calcifications of the wall of the gallbladder (7, 10). Fine punctate calcifica-

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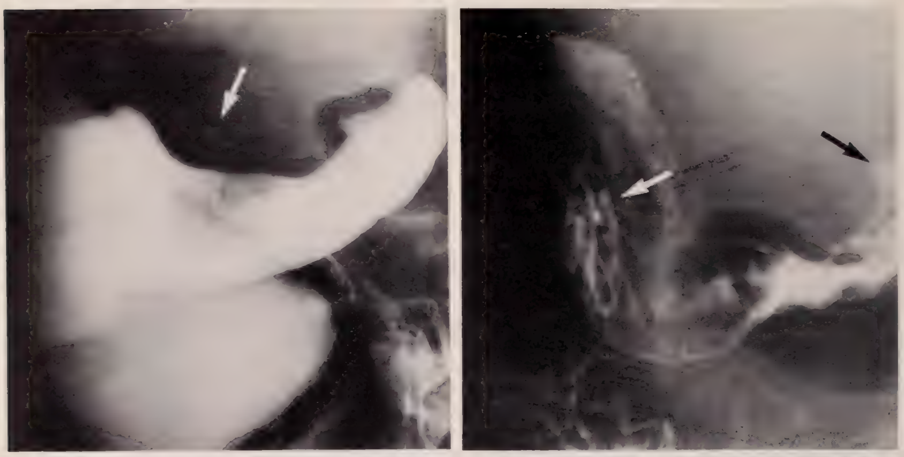

Fig. 1. **Left** Film from barium enema demonstrates mass compressing superior aspect of transverse colon (arrow). Smooth radiolucency is noted in region of mass. **Right** Postevacuation film demonstrates considerable distortion and fixation of mucosal folds (arrows).

tions in the right upper quadrant have been found in the adenocarcinomas (11).

The features of gallbladder carcinoma on upper gastrointestinal examination reflect its topographical relationship to neighboring structures (12). As a result, the lateral and superior aspects of the postapical part of the duodenal bulb are flattened and irregular, due to the extrinsic mass (Fig. 2). The superior segment of the duodenum is displaced inferiorly and the descending duodenum (second portion), when it is affected, is displaced backward or compressed anteriorly and laterally. Displacement of the duodenum and stretching of the duodenal folds indicates extrinsic pressure, whereas mucosal distortion, fixation, and narrowing all point to malignancy. Carcinoma of the pancreas, by contrast, affects the medial aspect of the sweep and bulb. Radiologic changes in the proximal transverse colon are less common but may demonstrate extrinsic

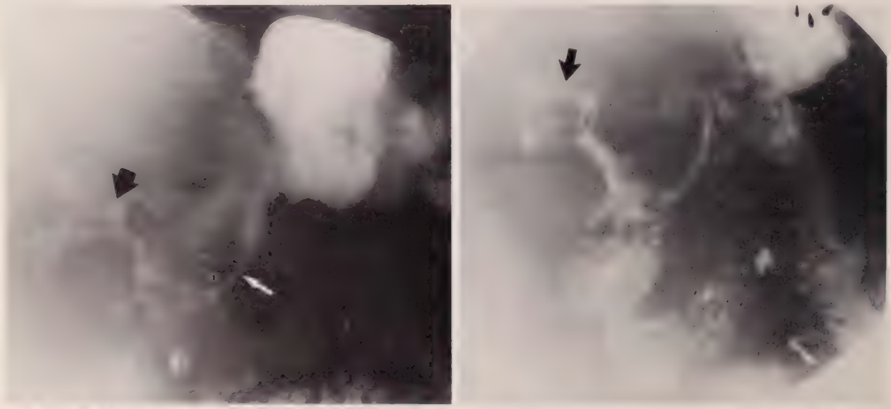

Fig. 2. **Left** Upper gastrointestinal series reveals extrinsic mass compressing postapical segment of duodenum and distorting mucosal folds (arrowhead), extravasation of contrast into mass (arrow). **Right** Two defects are evident in extravasated contrast material, suggesting presence of gallstones (arrow).

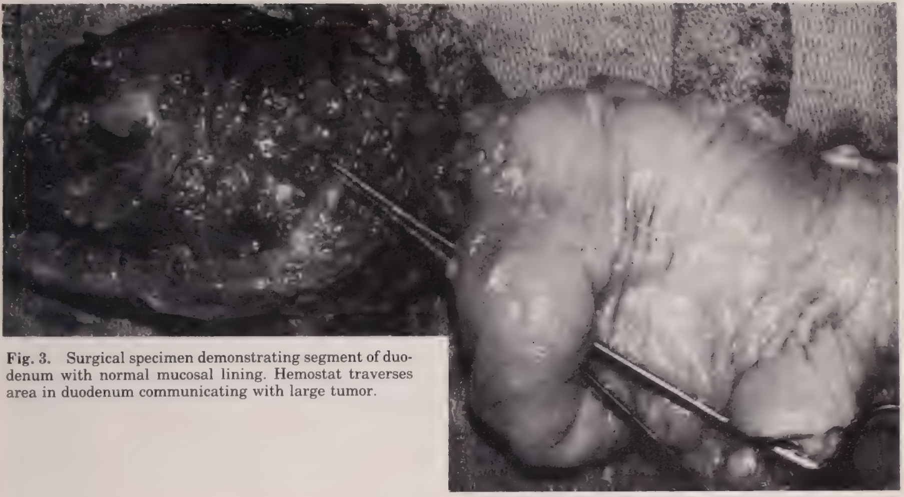

Fig. 3. Surgical specimen demonstrating segment of duodenum with normal mucosal lining. Hemostat traverses area in duodenum communicating with large tumor.

compression along the superior aspect, with fixation and narrowing indicative of infiltration by tumor.

Newer imaging modalities have been utilized in an attempt to diagnose gallbladder malignancy earlier. Features of its sonographic appearance include demonstration of a mass in the gallbladder in lieu of bile, localized or diffuse gallbladder wall thickening, and an intraluminal polypoid mass (13, 14). Tumor on computerized tomography has a variety of appearances and can be seen as a density representing discontinuous or irregular thickening of the gallbladder wall or an intraluminal mass (15). Both CT and ultrasound are well suited for demonstrating the extent of tumor invasion into the surrounding tissues (15).

In differential diagnosis, an alternative but less likely explanation for the patient's radiographic findings is a primary colonic carcinoma that fistulized to the duodenum and gallbladder. Colon cancer is a more frequent malignancy than gallbladder cancer and accounts for a sizable share of annual cancer deaths (16). Only rarely, however, does the lesion invade adjacent organs (17).

The most common radiographic appearance of colon carcinoma is an annular constricting lesion with nodular margins and mucosal destruction. Other patterns are polypoid, infiltrating or stenosing, and ulcerative.

When colon carcinoma perforates, it occurs either as "free" perforation into the abdominal cavity, "covered" perforation with local abscess formation, or perforation into neighboring organs with fistula formation. In one study these patterns were encountered in 5.4% of 836 cases of carcinoma of the colon, but occurred mainly on the left colon (18). Fistulae to the duodenum are rare (19) and invasion of the gallbladder appears to be even more unusual, although involvement of the extrahepatic biliary system does occur (20).

Diagnosis: Necrotic tumor of the upper abdomen, most likely primary gallbladder carcinoma.

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Radiology Notes *Jack G. Rabinowitz, M.D. Editor*

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Case 2

ELLEN S. GENDAL, M.D., RHONA J. KELLER, M.D., A. SICULAR, M.D., JEROME D. WAYE, M.D., AND A. CORNELL, M.D.

Case Report. A 74-year-old woman was transferred to The Mount Sinai Hospital from another institution with a five-week history of nausea and vomiting, 10–15 pound weight loss, fever, and chills. No melena or hematemesis was reported. Erythrocyte sedimentation rate was 113 mm/hr, alkaline phosphatase 580 mu/ml, hemoglobin 10.6 gm/100 ml, with normal red blood cell indices, and a white blood cell count of 27,100. Plain films of the abdomen demonstrated a persistent radiolucency with peripheral soft tissue indentations in the right upper quadrant. An upper gastrointestinal series performed previously revealed a large irregular collection of barium replacing the entire body of the duodenal bulb. There was also associated deformity and extrinsic compression of the postbulbar segment.

At The Mount Sinai Hospital a hepatobiliary nuclear ("hida") scan revealed multiple defects throughout the liver as well as nonvisualization of the gallbladder. The findings were thought consistent with metastatic disease and cholecystitis (acute or chronic). An abdominal sonogram demonstrated stones in the gallbladder and multiple solid liver masses without dilated ducts. Endoscopic retrograde choledochopancreatography showed a huge necrotic ulcerated mass in the duodenal bulb, biopsies of which revealed leiomyosarcoma. Laparotomy demonstrated the ulcerated tumor as well as purulent fluid in the peritoneal cavity. A palliative gastrojejunostomy with end-to-side antecolic anastomosis was performed, with prepyloric stapling of the stomach.

The postoperative course was stormy. The patient developed sepsis and died on the fifth postoperative day.

Discussion. The small bowel is the site of less than 2% of all gastrointestinal malignancies. The most prevalent malignant tumor is adenocarcinoma, followed in decreasing order by carcinoid, leiomyosarcoma and lymphosarcoma. Rare cases of fibrosarcoma, malignant schwannoma, liposarcoma, and angiosarcoma have been reported (1). Leiomyosarcoma of the small bowel was first described by Wesener in 1883, as a duodenal lesion (1). In a series of 421 cases reviewed by Wilson et al, the tumor sites were 10% duodenal, 37% jejunal, 53% ileal, and 1%–2% Meckel's diverticulum (1).

No risk factors for leiomyosarcoma of the small bowel are known, and no diseases are strongly associated. The peak age of presentation is the fifth to seventh decades, although no age is immune. The mean duration of symptoms preoperatively ranges from 14 to 23.3 months (2, 3). The main symptom is vague abdominal pain. Other common symptoms include weight loss, weakness, vomiting, and melena. Common clinical signs include guaiac-positive stool, anemia (often iron-deficiency type), leukocytosis, and abdominal distention. Twenty-five percent to 43% of patients have a palpable abdominal mass. Obstruction may occur (1, 2). Patients may occasionally have free perforation and peritonitis, particularly with exoenteric tumors. Anemia is secondary to hemorrhage from ulcerating tumors; fever and leukocytosis may be due to extramural abscess formation within a cavitating tumor, or tumor necrosis.

The radiologic findings on plain abdominal films include small bowel obstruction, soft tissue mass, and localized collections of gas with irregular margins that do not correspond to normal viscera or replace normal viscera, indicating cavitation or ulceration within necrotic tumor (4). On upper gastrointestinal series with small bowel follow-through, a submucosal lesion presenting as a contour defect is commonly found. Superficial ulceration is frequently associated with this lesion. Occasionally the mass appears as a pedun-

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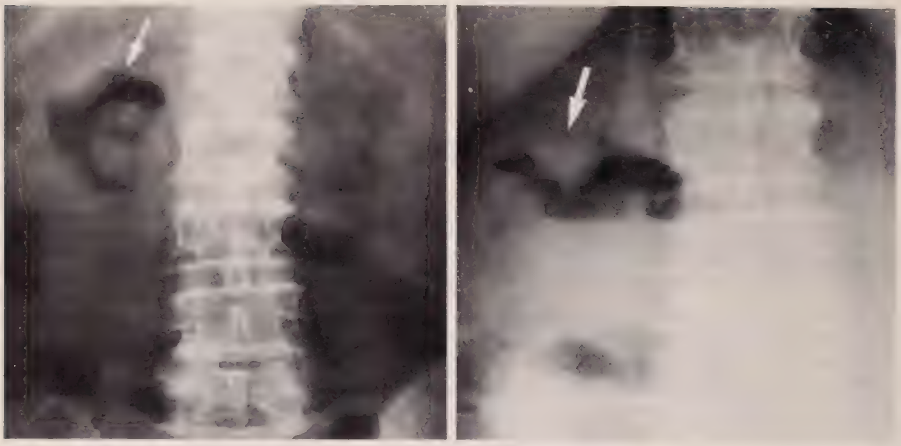

Fig. 1. **Left** Plain film demonstrates persistent triangular radiolucency with lobulated margins in right upper quadrant (arrow). **Right** Film of patient in upright position: radiolucent area is once more identifiable, unchanged in position.

culated intraluminal filling defect that may be associated with intussusception (1). The more commonly localized subserosal lesions, however, appear as large exoenteric masses which displace, separate, and compress loops of bowel. These leiomyosarcomas may also cavitate, fistulize, or perforate. By conventional methods, such as plain film and barium contrast studies, only 50%–60% of diagnoses of leiomyosarcoma are preoperative (5). Leiomyomas and leiomyosarcomas may be hypervascular, and angiography may be of use in detecting their extent. Using these studies, the sarcomas appear generally larger than anticipated, with poorly defined margins. Invasion of the neighboring organs as well as hepatic involvement may be noted. The tumors, because of their size, will stretch and splay neighboring vessels (6).

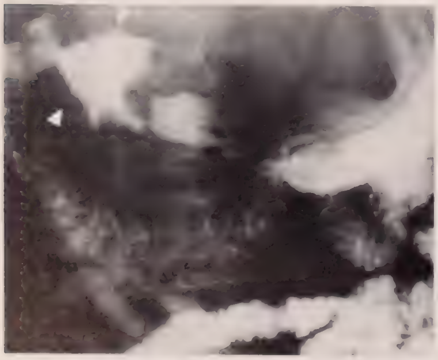

Fig. 2. Upper gastrointestinal series demonstrates large, irregular ulceration replacing duodenal bulb (arrows); extrinsic mass compresses postapical duodenum

Sonographic features of gastrointestinal leiomyosarcoma have been reported by Kaftori et al (7). All five patients in Kaftori's series had a palpable abdominal mass. A thick echogenic rim and a central mainly sonolucent area of cavitation was noted in four of the patients (7). Peroral endoscopy is limited to localization and biopsy of proximal lesions.

The tumor is generally lobular, sessile, or pedunculated and large, 76% being greater than 5 cm in diameter. Grossly the tumors have a "fish-flesh" appearance typical of sarcoma. A capsule may or may not be present. The smaller lesions may feel firm although as the tumors enlarge they become soft secondary to central necrosis (8).

The origin of a leiomyosarcoma is most often the muscularis propria. Rare cases arising from muscularis mucosa and from blood vessels of the bowel wall have been reported. Most lesions (63%) grow in an exoenteric fashion, in a subserosal location. Others may be submucosal and grow either toward the lumen, endoenterically (23%), or endoexoenterically in a dumbbell configuration (9). Exoenteric lesions grow very large and may actually lose their bowel attachment and become mesenteric masses (4). Microscopically leiomyosarcomas consist of spindle-shaped cells with elongated hyperchromatic nuclei and eosinophilic cytoplasm. Palisading nuclei may be seen. Evidence for malignancy includes the high number of mitoses, increased cellularity of the tumor, cellular pleiomorphism, and frank anaplasia (10).

Metastases occur by direct invasion of local organs and the retroperitoneum. Hematogenous spread is most common to liver, followed by lung, bone, and peritoneum (9). Lymphatic spread is extremely rare.

The site of the primary lesion in the small bowel has no influence on the overall prognosis of the patient. However, in addition to the pathologic classification, the clinical staging is also important. Stage A tumor is limited to the bowel wall and has, obviously, the best prognosis. Stage B involves the periintestinal tissues, and in Stage C nodal or distant metastases are present (3).

The definitive treatment of leiomyosarcoma of the small bowel is wide surgical resection for curative purposes. At laparotomy 24%–35% of patients already have metastatic disease. Palliative surgery is still recommended in the face of a nonresectable tumor, especially as leiomyosarcoma is considered to be slow-growing. The role of lymphatic dissection is controversial. Some authors find it unnecessary due to the infrequency of lymphatic spread (8, 11). Others, however, support the use of wider, more radical resection, including the adjacent mesentery (5).

Diagnosis: Primary leiomyosarcoma of the duodenum.

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Evoked Potentials in the Diagnosis, Prognosis, and Management of Neurologic and Neurosurgical Patients

NATHAN MOSKOWITZ, M.D., PH.D.

Abstract

Evoked potentials which record slow wave activity of the brain in response to visual, auditory, and somatosensory stimuli have recently been employed in the diagnosis of a variety of neurologic disorders and in the intraoperative management of patients undergoing neurosurgical procedures. The physiological basis, techniques, and clinical application of the variety of sensory evoked potentials employed are outlined and described here.

Slow waves of the brain represent the momentary fluctuations of the membrane potentials of neurons, and hence the probability of neuronal discharge (1). Therefore, monitoring of the continuous oscillating slow-wave activity of the brain provides an accurate evaluation of the average excitability of single nerve cells in the immediate vicinity of an electrode placed at or near the brain (2). This monitoring can be accomplished by both EEG and evoked potentials (EPs). The EEG records the spontaneous constant brain activity by summating the membrane and local potentials from large numbers of individual neurons located in various cortical and subcortical planes (3). The evoked potential differs from the EEG in that it records minute voltage changes produced only in response to a particular stimulus, auditory, visual, or somatosensory (4). The signal recorded by the EEG ranges in amplitude from 5 to 100μV, whereas EPs are less than 5μV and can only be detected by an averaging computer.

The evoked potential is a sensitive, objective, and noninvasive technique that has recently begun to play a serious function in neurologic diagnosis and prognosis, providing essential data to both neurologist and neurosurgeon (5). The value of EPs lies in the fact that they can provide a sensitive quantitative measure of sensory function in patients who are incapable of describing their sensory experiences—the infant, the anesthetized, and the comatose. This paper describes the variety of sensory EPs and illustrates applications in neurologic diagnosis and neurosurgical management.

Somatosensory Evoked Potentials

Description. Somatosensory evoked potentials (SSEPs) are elicited by electrical stimulation of peripheral nerves and can be used to infer the functional integrity of the peripheral nerve itself, the ascending spinal cord pathway and brainstem, the thalamus and specific cortex, as well as the nonspecific cortex (4). Peripheral nerve integrity is assessed by recording EPs from skin electrodes overlying the nerve. The presence of a slow-conduction velocity as evidenced by latency in the EP is evidence of a peripheral disorder.

The integrity of the ascending spinal cord pathway and brainstem can be detected by electrodes placed on the skin surface overlying the spinal cord; EPs in this area derive from activity in the peripheral nerve, dorsal columns and medial lemniscus, and diencephalic and cerebellar somatosensory pathways. Lesions of the anterolateral spinal tract that cause loss of sensations

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This paper was written when the author was a third-year medical student at Mount Sinai School of Medicine. Address correspondence to the author at Johns Hopkins Hospital, Dept. of Surgery, 655 Blalock, Baltimore, MD 21205.

of pain and temperature produce normal SSEPs. Only lesions in the dorsal columns resulting in loss of vibration and position sense alter SSEPs to pathological forms.

The role of the thalamus and cortex in the somatosensory impulse is assessed by recording EPs from the scalp 15 to 65 msec after stimulation of a peripheral nerve in the upper extremity. These EPs derive from the activation of specific sensory areas within the cerebral hemispheres, and their amplitudes are maximal in the scalp regions overlying the primary sensory motor cortex contralateral to the stimulated limb (6).

SSEPs can be influenced by the waking state of the patient (7), but not by the degree of the patient's senescence (8) or by the stimulus strength (4).

Clinical Application. SSEPs are useful in assessing advanced peripheral neuropathies in patients in whom compound nerve action potentials are difficult to detect (9). The recording of ascending activity to the spinal cord from the spinal column has been employed to detect the level of spinal pathology in infants (10).

SSEPs have been used in the operating room to monitor spinal cord function during operations on the spine and spinal cord which entail laminectomy for removal of spinal cord tumors or correction of spinal cord curvature. SSEPs have provided important information to surgeons on spinal cord function and have helped prevent some undesirable side effects of the operative manipulation of the spinal cord (11). Grundy et al (5) report the prevention of postoperative paralysis using SSEP monitoring in a patient being operated on with a large arteriovenous malformation lying on the corpus callosum. It was uncertain whether the anterior cerebral artery, the feeding vessel of the AV malformation, should be ligated. This artery provided the main blood supply to the sensory motor strip for the lower extremities and its ligation could induce paraplegia. After monitoring for normal SSEPs the operation proceeded, and the patient remained neurologically intact postoperatively.

SSEP monitoring has also detected intraoperative hypoxia (12) in a patient with syringomyelia and progressive spinal cord dysfunction undergoing cervical laminectomy. Surgical monitoring in addition to SSEPs included ECG, esophageal stethoscope, precordial Doppler, temperature, and central venous and intraarterial pressures, as well as intermittent measurements of blood gases, hematocrit, and osmolarity. At the conclusion of surgery only SSEPs provided the initial evidence of hypoxia, when its waves were distorted. Although the authors maintained that this information could have been derived from blood gas analysis, if SSEPs were not monitored and hypoxia were prolonged, harm could have come to the patient.

Thus SSEPs provide the neurosurgeon with essential information on the physical condition of the neuronal structures which are being manipulated as well as the systemic metablic condition of the patient.

Visual Evoked Potentials

Description. The stimuli employed to elicit visual evoked potentials (VEPs) include diffuse, patterned, and colored lights (4). The rate of stimuli presentation, the portion of the visual fields stimulated, and monocular or binocular presentation all modify VEPs (13). Retinal potentials (electroretinogram) are evoked by a diffuse light flash and can be detected by electrodes placed directly on the sclera or cornea, or on the skin surface close to the eye (4). These potentials reflect the function of the rods and their retinal connections. Scalp-derived VEPs, however, describe the function of the cones and their central projections. Occipital cortex function is deduced from occipitally derived scalp VEPs occurring 140 msec after presentation of diffuse light flashes (14).

With this type of stimulus, the stimulus intensity, the level of patient arousal, and electrode location all influence VEPs (15–17). Therefore, VEPs recorded in response to contrast patterns have become more popular because they are more reliable in both frequency and form and because the location of the electrode and the intensity of the stimulus have minimal effects (18, 19). VEPs are modified by changes in the location of the pattern of the visual field and by altering the stimulation to the upper or lower halves of the visual fields.

Clinical Application. VEPs can define ocular function and have proven of value in the selection of corrective lenses for children with astigmatism, thereby preventing amblyopia (20). Abnormalities have also been detected in patients with visual loss due to demyelination or to optic nerve involvement from tumors (21, 22).

In one situation Dr. Bodis-Wollner used VEPs to rule out the diagnosis of multiple sclerosis in a patient complaining of walking difficulties and pain around the chest whose routine x-rays and CAT scan were normal. VEPs were performed to investigate the possibility of multiple sclerosis and were shown to be within normal limits (5).

At that stage a myelogram was performed, despite a negative CAT scan, and displayed a benign operable spinal cord tumor.

In the operating room, flash-evoked potentials have been employed to measure optic nerve function during operation on patients with orbital or chiasmatic lesions (23). VEPs increased in amplitude following removal of tumors compressing the optic nerve (24). In addition the sudden appearance of VEPs has been described in the course of surgery in patients with pituitary tumors who had been without vision or VEPs prior to surgery (11).

Auditory and Brainstem Evoked Potentials

Description. Auditory evoked potentials (AEPs) are elicited by clicks or brief tone bursts that can be varied in intensity, frequency, and duration and in monaural or binaural presentation (4). The integrity of the cochlea and its hair cells and of the eighth nerve can be assessed by the placement of an electrode in the middle ear on the cochlea, or by scalp electrodes located in the ear canal or on the mastoid of the stimulated ear (25, 26). Electrical activity of the central auditory pathway can be recorded from scalp electrodes if many stimulus presentations are averaged. The resultant potentials are termed auditory brainstem evoked potentials (ABEPs) (27). The integrity of the thalamus and auditory cortex can be assessed by EPs (detected by scalp electrodes) occurring from 10 to 50 msec after presentation of flickered clicks or brief tones (28). Auditory evoked potentials are modified by the stimulus intensity, frequency, and repetition pattern (4).

Clinical Application. AEPs have provided an objective measure of audition (29) and have detected acoustic neuromas which were difficult to assess with standard audiometry (30).

ABEPs have assisted in the evaluation of structural damage to the auditory brainstem pathways due to tumors or demyelination or loss of circulation, and can distinguish between these structural alterations of the brainstem and metabolic alterations (31).

Stockard et al (32) have found that ABEPs could detect brain stem demyelination undetectable by other ancillary neurologic tests. They also found ABEPs useful in localizing neoplastic and vascular lesions to the peripheral, pontomedullary, pontine, midbrain, and thalamic levels of the auditory pathway. These same authors used ABEPs to monitor the evolution and response to therapy of brainstem tumors, contusions, and demyelinating and inflammatory processes, and to differentiate structural from metabolic etiologies of coma (32). Stockard et al (32) maintain that the fact that CAT scan has the highest false negatives in the posterior fossa suggests that ABEPs can supplement the radiologic assessment of this area.

Raudzens found that monitoring ABEPs gave good indexes of progressive auditory dysfunction during surgery, allowing continuous modification of surgical manipulations (5). In one situation, surgery in the auditory nerve region, the surgeon temporarily stopped what he was doing when ABEPs began to show pathologic changes, and the ABEP returned to normal. Thus ABEPs were employed in this situation, maintains Raudzens, to "prevent a reversible lesion from becoming an irreversible one."

Multimodality Evoked Potentials

MMEPs consisting of SSEPs, VEPs, AEPs, and ABEPs were found useful as a potential electrophysiological battery with which to localize dysfunction in individual neural systems (33). This method was of value in the evaluation and diagnosis of coma patients sustaining trauma. Greenberg et al classified patients with injuries in each sensory modality into functional Grades I-IV according to increasing abnormality. The authors (33) felt that the grading of the injury potential enabled them to define the degree of abnormality. VEPs and AEPs reported in comatose patients significantly correlated with retrobulbar visual dysfunction and auditory dysfunction from eighth nerve damage, and were more effective than neurologic examination in diagnosing dysfunction in the early traumatic period.

The same authors also found that using SSEPs in comatose patients predicted outcome and monitored brain function more reliably and accurately than did clinical examination, intracranial pressure measurements, or CAT scans (33). They maintain that the influence of secondary insults such as elevated intracranial pressure, pneumonia, meningitis, or septicemia can only be successfully determined by SSEPs in comatose patients.

Summary

EPs clearly show great promise in facilitating the diagnosis of acute neurologic and neurosurgical problems and great utility in intraoperative monitoring, facilitating more accurate dissections with fewer lethal sequelae. The decreasing cost of EP computerization and the increasing compactness of the computers used are making EPs more popular and more feasible in neurosurgical operating rooms. Knowledge of the physiological basis of EPs and their interpretation and evaluation may therefore soon become an essential part of the armamentarium of the physician.

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Arterioportal Fistula as Cause of Hypertension

DONALD PANG, M.D.

An unusual cause of portal hypertension is an arterioportal fistula. Such fistulas can occur at any site within the portal venous system and can originate from the splenic, hepatic, or mesenteric arteries. Arteriovenous fistulas can be the result of ruptured aneurysm, intraabdominal surgical procedures, or abdominal trauma such as a gunshot or a stab wound. A case of bleeding from gastric varices resulting from traumatic fistula between the splenic artery and gastroepiploic vein is presented.

Case Report. A 53-year-old man known to have a splenic artery to epiploic vein fistula since 1978 was admitted to the hospital because of abdominal cramps, hematemesis, and melena over forty-eight hours. The patient was also on hemodialysis for chronic renal failure. He was currently taking Catapres and Lopressor. He reported a gunshot wound to the left upper quadrant, ten years previously. He had no personal or family history of liver disease or pancreatitis.

On examination, he was acutely ill. His blood pressure was 180/100 supine and 150/80 upright. The pulse rate was 104 supine and 120 upright. His respiratory rate was 18 and his temperature 98.9. He had cardiomegaly with displaced apical beat to the sixth intercostal space and a 2/6 holosystolic murmur heard best at the apex with radiation to the aortic region. This murmur was believed to be a flow murmur with no signs of mitral valve insufficiency or aortic valve stenosis by echocardiography. Pulmonary examination was unremarkable. The abdomen was diffusely tender to palpation without organomegaly or masses. There were increased bowel sounds in all four quadrants, but no bruit was noted. Guaiac test was positive for both stool and vomitus. Pulses were strong and regular.

Laboratory evaluation disclosed the following findings: hemoglobin, 5.5 g/dl; hematocrit, 24.4%; WBC count, 11,200/cu mm with normal differential; serum urea nitrogen, 89 mg/dl and creatinine, 12.7 mg/dl. Coagulation studies were within normal limits.

Chest x-ray showed right-side cardiomegaly and mild pleural effusion without active pulmonary parenchymal disease. No esophageal or gastric varices were seen on upper gastrointestinal series. An aortogram taken in 1978 demonstrated a large tortuous splenic artery with a large fistulous communication to the gastroepiploic vein (Figs. 1, 2).

At laparotomy, a gastrostomy was performed; careful inspection of the proximal stomach revealed multiple areas of venous lakes consistent with arteriovenous malformations. One of these areas was excised and the base was pulsatile. There was no peptic ulcer, and as the stomach was further mobilized, an enlarged gastroepiploic vein was found running within the greater omentum. This vein was followed back to its point of origin, the splenic artery. The splenic artery was mobilized and cross-clamped. There was immediate decompression of the prominent veins in the greater omentum as well as complete control of the bleeding in the stomach. The splenic artery was then ligated, leaving the short gastric vessels intact. A liver-spleen scan done on the fifteenth post-operative day failed to visualize the spleen.

This article was written when the author was a third-year student at the Mount Sinai School of Medicine (CUNY). Address correspondence to the author at 3440 Balboa Street, San Francisco, CA 94121.

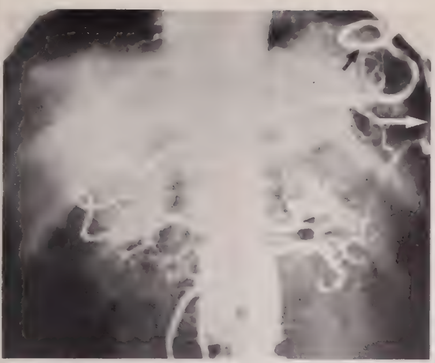

Fig. 1. **Left** Tortuous splenic artery (short arrow); early filling of fistulous communication between splenic artery and gastroepiploic vein (long arrow).

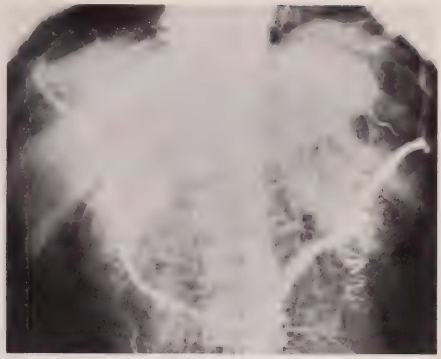

Fig. 2. **Right** Late filling of arteriovenous malformation showing enlarged arteriolized gastroepiploic vein coursing through greater omentum.

The patient had no recurrences of hematemesis or melanotic stools. He remained in the hospital for six weeks after surgery for further management of his chronic renal failure.

Discussion. Arteriovenous fistula of the portal system is an unusual cause for portal hypertension. I found only 30 reported cases with a splenic arteriovenous fistula, which constitutes approximately one in three of arteriovenous fistulas within the portal system. Bredfeldt and O'Laughlin reported rupture of a splenic aneurysm (21 cases), splenectomy (3 cases), gunshot wound (2 cases), mycotic (1 case), and splenoportography (1 case) as etiologies of arteriovenous fistula within the portal system (1). The age of the patients ranged from 13 to 82 years (average 44). Women outnumbered men by a factor of three; this predilection for women seems to correlate with the increased incidence of splenic artery aneurysms and multiple pregnancies.

Arida categorized the different clinical presentations of 23 cases of portal splenic arteriovenous malformation. Of the 23 cases, 8 had demonstrable esophageal varices; only 2 of these had murmurs or bruits discovered on auscultation of the area, and 10 patients had gastrointestinal bleeding, most with hematemesis (3). The bruit may be either systolic or "machinery" usually heard in the left upper quadrant. Despite portal hypertension and splenomegaly, signs of clinical liver disease are conspicuously absent, and the hepatic venous pressure gradient is normal or slightly elevated.

Arteriovenous fistulas can often present a diagnostic dilemma, if a bruit is absent. Though the hepatic venous pressure gradient was not known in this patient, clinically the patient manifested portal hypertension with intragastric varices. The opportunity to cure this cause of gastrointestinal bleeding obviously depends on recognition of the causative factor, namely the fistula. Although this is an admittedly rare abnormality, it should be suspected in all cases of portal hypertension with normal liver function and absence of stigmata of hepatic cirrhosis. Certain aspects of the patient's history can lead one to suspect an arteriovenous malformation. These include a history of demonstrated splenic artery aneurysm, blunt or penetrating abdominal trauma, multiple pregnancies, or most importantly, prior surgery.

Selective arteriography of the celiac or splenic artery should be used to search for splenic arteriovenous fistulae (4).

Evaluation with plain abdominal radiographs may demonstrate ascites or splenomegaly if present. One may see a calcified splenic artery aneurysm. Contrast studies of the upper gastrointestinal tract may be of value in demonstrating esophageal or gastric varices.

Summary. This etiology of portal hypertension is unique in that it is ameliorated by simple surgical ligation of the arteriovenous malformation. This case report illustrates the necessity of careful preoperative evaluation in a patient with portal hypertension, and the methods one could use to detect an arteriovenous malformation.

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Corrections

The June 1984 issue (vol. 51, no. 3), article "Complementary Effect of Cholecystokinin-octapeptide and Soy Flour Treatment in Chronic Pancreatitis," by Akos Pap, Zolton Berger, and Vince Varro. The following corrections were received from the authors after the issue was published:

page 254, column 1, last line, sentence reading "Some preliminary data has already been presented (7)": Citation should be (8).

page 255, column 1, under head Treatments, line 6: The amount of raw soy flour administered was 30 gm, not 3 gm.

page 255, column 2, under head Results, lines 17–19: The effect of CCK-OP was more pronounced than the effect of soy flour in the two soy responders, not the two soy nonresponders.

Letters to the Editor

The Mount Sinai Journal of Medicine
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The Graffiti Pharmacopeia

To the Editor: I have been seeing the names of medications scrawled on the walls of New York City. I am referring to that inner-city form of urban expression usually associated with spray-paint guns and a psychologic admixture of attention-seeking and vandalism: graffiti.

Perhaps you think I am hallucinating or somewhat paranoid. But I tend to think not, considering my firm base in reality and the intensity with which detail people have been forcing pens, flashlights, dessicated sponges, etc., onto my person in the name of product promotion. Most likely, though, this phenomenon represents my projection of professional musings onto this potpourri of words and letters, just as a young lover might see his paramour's initials in a car's license plate. Nonetheless, I submit a few examples for your contemplation.

Two blocks from a large downtown medical center I found a two-block area elaborately decorated with numerous graffiti monikers; one in particular—*Atarax*—stands out. Who is responsible for this one? I find it difficult imagining our intrepid Roerig detailman, polyester suit, too-wide tie, spray-paint can in hand, nervously glancing over his shoulder as he finishes off another masterpiece. Yet I also cannot see him buying off a twelve-year-old youth with electrocardiogram calipers and a paperweight that bears a vague semblance to the limbic system.

Could there really be something inherent in a name? The product's name was chosen by experts looking for something that sounded good, would sell their agent, and might subliminally suggest that it provides "symptomatic relief" for those suffering from certain afflictions. Could the psyche of some youthful spray-gun wielder have independently latched onto the pleasant nuances suggested by this word?

The drug industry's battles seem to have spilled over into the urban advertising arena. Some of our New York graffiti artists seem less bent on plastering trade-name sobriquets onto walls in day-glo than on trumpeting their support of generic medications. On a wall one block from a large Upper East Side hospital run by New York City is the exclamation *ASA*. I have considered the theory that graffiti memorialize the particular drugs that each artist abuses on a recreational basis. Though such an explanation has its merits, I tend to reject it. Even though many drugs (some quite unexpected) have been abused, I find it hard to believe that anyone would tout the joys of salicylism.

The most riveting of the pharmacologic graffiti I have seen awaits me at the end of my journey home from my tour of duty at the hospital. On my garage door, the door that protects my car from the ravages of the city, large white letters display the acronym *DES*. Can it be that somewhere a sane, rational spray-paint artist, troubled by the proliferation of wanton medication use, attempts to make us pause and reflect on the possible ills of profligate medication prescribing and imbibing? Remember, after all, that the street giveth and the street taketh away.

STEPHEN J. MARKS, M.D.
written from Mount Sinai Medical Center
now at Duke University Medical Center
Durham, NC 27705

Letters to the Editor: Letters should be short and will be subject to editing. Objective, constructive criticism of published articles or discussions of questions of general interest in medicine are welcome. Double-space the text of the letter and any accompanying references or tables.

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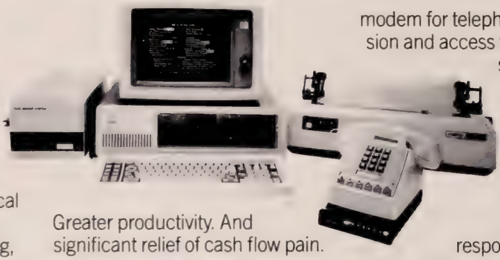

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CONTENTS

Editorial 649

The Relationship of Hyperactivity of the Duodenal Autonomic Nervous Brain (Duodeno-Pancreatic Reflexes) and Enhanced "Pancreon" Secretory Response to CCK-PZ in Chronic Alcoholism *Osvaldo M. Tiscornia, M.D., Carlos J. Perec, M.D., David Celener, M.D., Miguel A. Cresta, M.D., Omar R. Tumilasci, M.D., Enriqueta S. de Lehmann, M.D., and David A. Dreiling, M.D.* 650

Trophic, Biochemical, and Functional Changes in Submaxillary Glands and Pancreas Induced by Chronic Alcohol Feeding Mediated by Parasympathetic Autonomic Centers *Carlos J. Perec, M.D., Osvaldo M. Tiscornia, M.D., Carlos M. Baratti, M.D., Omar R. Tumilasci, M.D., and David A. Dreiling, M.D.* 664

^{3}H-QNB Binding in Submaxillary Glands Subsensitized by Chronic Alcohol Feeding *Irma C. W. de Peusner, Carlos J. Perec, M.D., and Osvaldo M. Tiscornia, M.D., FACG* 675

The Effect of DL-Ethionine, Cholecystokinin, and Cerulein on Pancreatic Secretion and Tissue Composition in Rats *Miklós Papp, M.D. Sc.D., Gábor Varga, István Fodor, M.D., C. Sc., Dezsö Szabo, M.D., C. Sc., and Gábor Folly* 680

Contents continued inside

THE
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JANUARY

Medical, Surgical, and Gynecologic Complications of Pregnancy

Editor: Sheldon H. Cherry, M.D.
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Volume 51
Number 6
December 1984

CONTENTS *continued*

Response of Plasma Norepinephrine Levels to Stimulation in Renovascular Hypertension *Abraham U. Waks, M.D., J. Francois Burkhalter, M.D., and Morton H. Maxwell, M.D.* 687

Dose-Related Nephrotic Syndrome in Penicillamine-Treated Rheumatoid Arthritis *Harry Spiera, M.D.* 695

Diagnosis of Polar Hypertrophy of the Kidney Revisited *Luis O. Martinez, M.D., FACR, David A. Francis, M.D., Kathy J. Schilling, M.D., and Bradley M. Cohen, M.D.* 697

Surgical Management of Duodenal Duplication Cyst Simulating Pyloric Stenosis *Joseph M. Pober, M.D., and Michael A. Bleicher, M.D.* 702

Synovial Sarcoma of the Anterior Abdominal Wall *Eric N. Faerber, M.D., John C. Leonidas, M.D., and Ina Bhan, M.D.* 705

The Papago Indians: Historical, Social, and Medical Perspectives *Benjamin H. Hoffman, M.D., and Alexa J. Haskell, M.A.* 707

PATHOLOGY NOTES *William Thomas Jr., M.D., editor*

Ultrastructural Study of the Faces of Diseases *Marcelino G. Reyes, M.D., and Kimi Teramura, M.S.* 714

Cholesterol Emboli Causing Acute Gangrenous Cholecystitis *William Thomas, Jr., M.D., and Philip Zaret, M.D.* 716

SURGERY NOTES *Leo Gordon, M.D., editor*

Duplex Scanning of the Carotid Arteries *David Cossman, M.D., Richard Treiman, M.D., J. Louis Cohen, M.D., Phillip Levin, M.D., and Robert Foran, M.D.* 718

continued

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GREATER MIAMI

CONTENTS *continued*

STUDENT'S CORNER

Gastric Carcinoma in the Young: Overview of the Literature *Mark G. Schwartz, M.D., and Nicholas A. Sgaglione, M.D.* 720

Clinical and Pathologic Dilemmas in Tolosa-Hunt Syndrome: A Case Report *Michele T. Gallati, M.D.* 724

Late Dacron Graft Failure: Two Cases *Ian Ahwah, M.D.* 728

Index to Volume 51 732

Index to Advertisers

Allied/Regency Medical Laboratories	cover 3
Blue Cross and Blue Shield of Greater New York	cover 4
IHM Institute for Health Maintenance	i

THE MOUNT SINAI JOURNAL OF MEDICINE
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Editorial

With this final issue of the 1984 year, it seems to me timely to report to our readers on the state of the *Journal* after one year of our new arrangement, the affiliation with our publication of Cedars-Sinai Medical Center, Mount Sinai Medical Center of Chicago, and Mount Sinai Medical Center of Greater Miami.

Our hopes that the *Journal* would flourish under this new arrangement have indeed been confirmed.

The reviewing process has been invigorated by the panels of reviewers at each of the three institutions; the reviewers have been both energetic and discriminating in behalf of the *Journal*.

Our bank of manuscripts has been augmented by authors new to the *Journal*, reporting on material which is, as we hoped, enlarging and varying the scope of medical topics addressed in our pages.

Our Notes columns have also been augmented by new editorial energy, and we have been able to expand the disciplines covered by these Notes. We have adopted the practice of running our Notes columns under the name of the editor submitting the material wherever we have more than one Notes editor for a particular specialty.

The contributions of our new affiliates are now beginning to surface in printed form. In this issue, for example, the Notes sections are entirely the work of our new affiliates, and we present an article from Cedars-Sinai (Abraham Waks et al on norepinephrine in renovascular hypertension), and one from Miami (Luis Martinez et al on diagnostic differentiation of polar hypertrophy of the kidney and neoplasm). A number of articles from our affiliates are awaiting publication, or are still under review.

We are moving toward monthly publication. This year the *Journal* has published 784 pages—an increase of some 200 pages over each volume since 1979, and the page equivalent of over 8 issues. In 1985 we plan to publish 9 issues.

Our financial health has been augmented by three new advertisers, bringing our advertising revenue to double what it was in 1983 (albeit from a modest base). What has attracted advertisers is the national readership of 6,000, as well as the loyalty of our Mount Sinai Medical Center of New York reader-subscribers. We trust this advertising revenue will continue to increase as the new affiliation arrangement is solidified, giving the *Journal* a financial base upon which to expand our scope.

The Mount Sinai Medical Center of New York has offered the *Journal* larger and more attractive offices at 5E, 19 East 98th Street, and the editorial and business office has just begun operating from that new address.

For the success of our new venture in institutional editorial cooperation, we must thank not only our longstanding editorial supporters in New York, but also the liaison people at each of the new affiliates—Leon Morgenstern and Deena Bailey at Cedars-Sinai Medical Center; Maxwell Westerman, Benn Greenspan, and Norbert Gleicher at Mount Sinai Hospital Medical Center of Chicago; and Federico Justiniani and Philip Samet at Mount Sinai Medical Center of Greater Miami—as well as our new reviewers and Notes editors, and all the researcher-authors who have already and will in the future be submitting manuscripts to the *Journal*.

DAVID A. DREILING, M.D.
Editor-in-Chief

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The Relationship of Hyperactivity of the Duodenal Autonomic Nervous Brain and Enhanced "Pancreon" Secretory Response to CCK-PZ in Chronic Alcoholism

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OMAR R. TUMILASCI, M.D., ENRIQUETA S. DE LEHMANN, M.D., AND DAVID A. DREILING, M.D.

Abstract

Graded doses of pilocarpine superimposed on basal bile-pancreatic secretion (BPS) "plateau" values in the rat either inhibit or do not modify the hydrelatic and ecbolic parameters. Atropine alone depresses all BPS measurements. Pilocarpine superimposed on BPS "plateau" levels, in atropine pretreated animals, induces a reversal phenomenon, which suggests involvement of VIP and/or other peptides or factors. This reversal does not occur in alcohol-fed rats. It is postulated that alcoholism elicits a ganglionic nicotinic receptor subsensitivity. This subsensitivity leads, on the one hand, to an enhancement of the intrapancreatic nonnicotinic nervous pathway normally activated by CCK-PZ and ethanol itself. On the other, the subsensitivity reduces the secretion of VIP and/or other peptides or factors, among them those with capacity to inhibit "pancreon" units that are normally released by CCK-PZ. The imbalance of the mechanisms that normally interplay to control exocrine pancreatic secretion may be the basis of the hyperactivity of the duodenal autonomic nervous brain (duodeno-pancreatic reflexes) and the enhanced "pancreon" secretory response to CCK-PZ in the chronic alcoholic stage. The results imply that it would make sense to treat this condition by depressing or shunting the duodenal autonomic nervous brain.

During testing (of rats) designed to elucidate the neuroendocrine mechanisms responsible for sequential changes in basal bile-pancreatic secretion (BPS) when it is diverted to the exterior, it was found, unexpectedly, that two series of graded doses of a cholinomimetic agent (pilocarpine) either inhibited or did not change secretory values. This prompted the hypothesis that an indirectly cholinergic pathway triggered the release of an inhibitory BPS factor and/or regulatory peptide. To provide evidence of such probable participation, we carried out tests superimposing graded doses of pilocarpine on an atropine-evoked BPS "plateau" level.

Moreover, it has been reported that alcohol-fed dogs (1–5) show a progressively decreasing influence of a probable regulatory peptide with cholinergic-dependent inhibitory capacity of exocrine pancreatic secretion (EPS). We therefore performed tests on rats fed with ethanol for 3, 6, and 12 months.

In addition, we have observed in truncal vagotomized rats (6) a notorious change of the BPS pattern that we have attributed to the loss of a probable cholinergic-dependent inhibitory mechanism. We therefore carried out tests on truncal

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vagotomized animals with and without graded doses of pilocarpine.

Materials and Methods

Experiments were performed on 117 male Wistar rats. Six series of experiments were analyzed. In all experiments the same bile-pancreatic fistula was performed.

Bile-Pancreatic Fistula. All the animals were operated on under ether anesthesia. After entering the abdomen through a midline incision, under the dissecting microscope a plastic catheter (diameter 0.65 OD) was ligated with 6-0 silk and the catheter secured with another ligature of the same material. The draining catheter was given a hook form. The tip of the short segment of the hook was bevelled to facilitate its entrance into the bile duct. A small hole was made in the catheter close to the tip opposite to the bevelled end, to prevent interruption of the bile-pancreatic flow if movements of the plastic catheter caused opposition of its tip against the hepatic duct wall. The long segment of the hook was brought to the subcutaneous level at the left side of the midline laparotomy. Its course was right to left, crossing the abdominal cavity in a horizontal direction under the liver and in front of the anterior surface of the stomach. Elongated by a silastic catheter, it was then brought to the neck through a subcutaneous tunnel. Another silastic catheter, 8 cm long, with several holes placed alternately around its circumference, was inserted through a small incision in the posterior wall of the duodenum close to the pylorus. At this level, it was secured by a purse-string suture. Elongated by another plastic catheter (diameter 0.65 OD) and after following a right-to-left course, it was brought to the subcutaneous level through the same incision previously performed at the left side of the midline laparotomy. From here, and through the subcutaneous tunnel, it was transferred to the neck. Marked elasticity of the silastic tube within the duodenum prevented deformation of the duodenal *C* form (Fig. 1).

This technical approach has two fundamental advantages. First, it permits unfolding of the mesoduodenopancreas through which the bile duct courses. This permanent stretching of the mesoduodenum by the intraduodenal silastic tubing prevents its shrinkage and retraction and, thus, avoids impairment of bile flow and pancreatic drainage through the several small ducts that enter the distal segment of the hepatic duct. Second, both the silastic intraduodenal tube inserted through the posterior wall of the first part of the duodenum and the modelling as a hook of the plastic catheter draining the bile duct allows normal positioning of the duodenum, a prerequisite to maintaining an unimpaired flow of the bile-pancreatic juice to the neck and its recirculation into the upper small bowel. A third tube, a plastic catheter having at its end a short segment of silastic, was placed in the peritoneal cavity and brought to the neck through the same subcutaneous tunnel followed by the bile and duodenal catheters. This peritoneal catheter was used to infuse, in the respective series, atropine, or pilocarpine alone, or atropine followed by graded doses of pilocarpine.

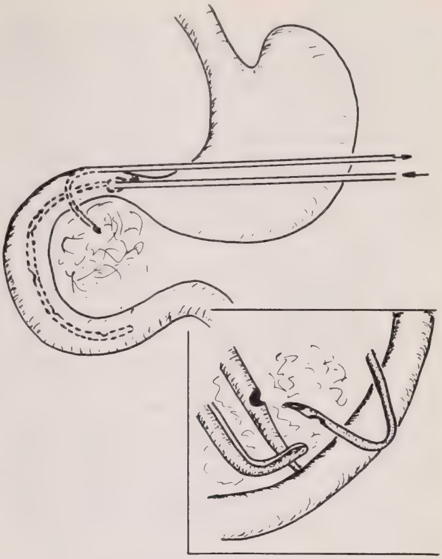


Fig. 1. Biliary pancreatic fistula.

In the vagotomized series, after isolation of the esophagus, the thin branches of the left or anterior vagus nerve were transected. The right or posterior vagal branch was sectioned between two ligatures of 6-0 silk. The surgical procedure was completed with a pyloroplasty. Within a period of 60–90 days the rats were reoperated on in order to perform the biliary pancreatic fistula as described for controls.

All surgical procedures were carried out during the morning hours, without previous fasting. Tests were performed in Bollman restricted cages. After the functional evaluation, both catheters in the neck were connected to each other to allow recirculation of bile-pancreatic juice into the gut and animals were transferred to their normal cages where they could keep a normal life, without any movement restriction, in fasting condition and drinking water ad libitum. Rats were tested during the first two days following surgery. Experience has shown that during this period the bile-pancreatic juice rate of flow is regular and reproducible. After 48 hs, when the test of this day had been completed, the animals were killed and autopsied.

Testing was always done during the morning hours, at room temperatures of 25–27°C. Rats were placed in a Bollman cage. The tubes in the neck were disconnected and the bile-pancreatic juice was collected in small calibrated tubes immersed in crushed ice; collection periods were 30 minutes each. The average values of the second and third periods were designated as the "plateau."

The atropine and pilocarpine injections were given through the intraperitoneal catheter placed in the neck behind the bile-pancreatic-duodenal connection.

The following parameters were chosen for the biochemical assays:

- Volume (ml in 30 minutes) was measured with a precision of 0.1 ml.
- Bicarbonate concentration (HCO_3^- mEq/1) was determined by the titrimetric method described by Lehmann et al (7).
- Bicarbonate output was calculated and expressed as μEq/30 min.
- Protein concentration was measured according to the method described by Gornall et al (8).
- Protein output was expressed as mg/30 min.

After secretory study, rats were killed under ether anesthesia. The pancreatic gland was dissected from the surrounding tissues and the head of the organ was isolated from the body-tail. The head was designated as the segment of the gland between the pylorus, the internal border of the duodenum, and a line drawn along the right border of the mesenteric vein and passing through the pylorus. The remaining gland was considered body-tail. The dissection of the gland was done carefully, with the aim of removing all the fat tissue and lymphatic glands which surround the body-tail. The pancreatic gland was blotted dry and weighed.

Statistical analysis consisted of calculating the mean and standard error of the mean of the results. These were expressed primarily as percentage change from the "plateau." The significance of the percentage change was evaluated using Student's *t* test for nonpaired values. P values less than 5% ($p < 0.05$) was interpreted as significant (9).

Experimental Series

Control. Seventeen animals were studied. The body weight was 416 ± 12.87 gm. Bile-pancreatic secretion was collected for 270 minutes. The average values of the second and third periods was considered as "plateau." Changes in the following periods were expressed as a percentage of the "plateau" level (Figs. 2–4, 8, 9, 13–18).

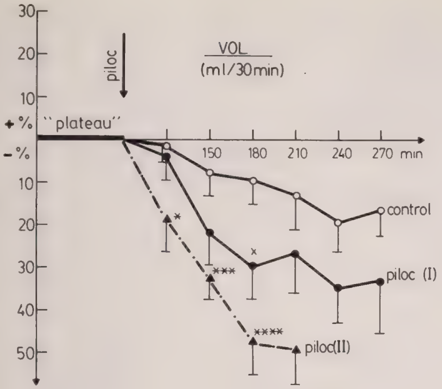
Atropine. In two series of animals atropine, at the dose of 0.3 mg/kg, was given intraperitoneally, within 30 minutes, following completion of the "plateau" stage. In the first series of 16 animals (387 ± 31.21 gm) the BPS percentage changes were analyzed for 60 minutes (Figs. 5–7). In the second series of 5 animals (378 ± 36.35 gm) the percentage of modifications from the "plateau" were pursued for 270 minutes (Figs. 8, 9).

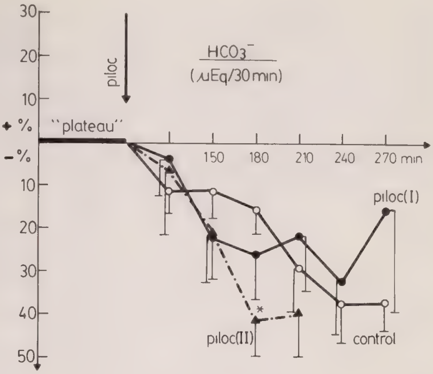
Pilocarpine. The cholinomimetic agent pilocarpine was administered by graded doses at the end of the "plateau" stage. Each dose was infused intraperitoneally within 30 minutes. Two series were performed on a total of 24 rats (414 ± 20.30 gm). In one series (17 rats) doses were small, ranging from 0.01 to 3.0 mg/kg. In the other series (7 rats) high doses, ranging from 3.0 to 100 mg/kg, were infused (Figs. 2–4).

Atropine plus Pilocarpine. In 15 animals (378 ± 36.35 gm) atropine was given intraperitoneally (0.3 mg/kg) at the end of the "plateau" period. Sixty minutes later, when the BPS parameters were maximally depressed, pilocarpine was administered intraperitoneally in graded doses ranging from 0.1 to 1.0 mg/kg (Figs. 10–12).

Vagotomy and Vagotomy plus Pilocarpine. Eleven animals (502 ± 27.21 gm) were subjected to truncal vagotomy plus pyloroplasty. In 11 tests, the spontaneous behavior of the BPS parameters (percentage changes in respect to "plateau") was evaluated (Figs. 13–15). In 8 animals (387 ± 26.45 gm) pilocarpine was given intraperitoneally by graded doses ranging from 0.1 to 10.0 mg/kg (Figs. 13–15).

Chronic Alcoholism. Three series of rats were subjected to three different period of alcohol intoxication: 3, 6 and 18 months, respectively. Animals were allowed to drink only a solution of ethyl alcohol according to the following schedule: first week 5% solution (v/v); the next two weeks, 10.0 (v/v); the following week, 15% (v/v); the fifth





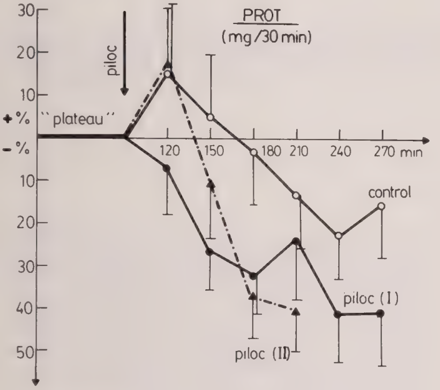


Fig. 2. Top left Rate of flow of basal bile-pancreatic secretion (EPS). Spontaneous and pilocarpine (piloc)-induced percentage changes in respect to "plateau" levels. Graded doses of cholinomimetic were given intraperitoneally at end of the "plateau" stage (first 90 minutes). (I) Low doses of piloc: 0.01; 0.03; 0.1; 0.3 and 1 mg/kg. (II) High doses: 3; 10; 30 and 100 mg/kg. Values shown are mean ± SEM. X-$p < 0.05$, low doses of piloc (n:7) compared with control values (n:17); * $p < 0.05$, *** $p < 0.01$ and **** $p < 0.001$, high doses of piloc (n:7) compared with controls (n:17). Each animal was subjected to only one test (n: number of observations).

Fig. 3. Top right Bicarbonate output of EPS. Key as in Fig. 2. * $p < 0.05$ when compared with control values.

Fig. 4. Left Protein output of EPS. Key as in Fig. 2.

week, dose increased to 25% (v/v) until on the 90th day the animals received a solution of 32% (v/v).

In 8 animals (465 ± 14.83 gm) alcohol-fed for 6 months, the spontaneous changes of the BPS were followed for 210 minutes (Figs. 16–18).

In 7 animals (417 ± 16.49 gm) alcohol-fed for 6 months, pilocarpine was given in graded doses superimposed on the "plateau" stage (Figs. 16–18).

In 6 animals (329 ± 22.44 gm) alcohol-fed for 3 months, graded doses of pilocarpine were superimposed on an atropine-induced "plateau" (Figs. 19, 20).

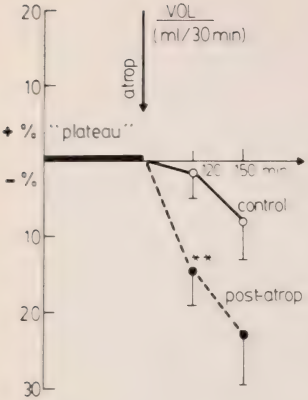
In 8 animals (430 ± 17.70 gm) alcohol-fed for 18 months, the same protocol of pilocarpine following atropine was applied (Figs. 19, 20).

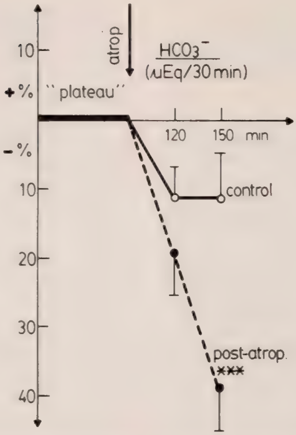
Results

Control Studies. The percentage changes following the "plateau" stage were analyzed in 17 animals, taking into account the secretory values of the first 24 hours of the biliary pancreatic fistula. Virtually all parameters of BPS showed a spontaneous progressive drop after the "plateau" period. The peak inhibition percentage drop for each parameter was as follows: volume, 19.45%; HCO_3^-, 28.08%; HCO_3 output, 37.82%; protein concentration, 7.7%; protein output, 23.28% (Figs. 2–4, 8, 9, 13–18).

Atropine. Blocking of the muscarinic receptors by atropine (0.3 mg/kg) at the end of the steady-state period ("plateau") induced depression of all BPS parameters. Forty minutes after administration of atropine the percentage fall in secretory values was as follows: volume, 23.22%; HCO_3^-, 20.41%; HCO_3^- output, 38.96%; protein concentration, 10.55%; protein output, 31.70% (Figs. 5–7).

In 5 rats the atropine-elicited percentage





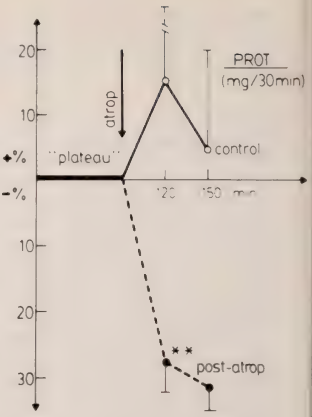


Fig. 5. **Left** Volume of EPS. Spontaneous and atropine (atrop)-induced percentage changes in respect to "plateau" levels. Atrop. (0.3 mg kg) given intraperitoneally in 30 minutes at end of "plateau" stage (first 90 minutes). Vertical bars are SEM of 16 observations. ** $p < 0.02$. Significant from same period of spontaneous changes in control animals (n:17). (n: number of observations: number of animals).

Fig. 6. **Center** Bicarbonate output of EPS. *** $p < 0.01$. Key as in Fig. 2.

Fig. 7. **Right** Protein output of EPS. ** $p < 0.02$. Key as in Fig. 2.

changes in rate of flow and protein output (bicarbonate was not determined) in respect to the "plateau" values were followed for 180 minutes. Figs. 8 and 9 show that the depression pattern was maintained for the whole experiment, although due to the spontaneous fall that occurs normally, the drop of BPS evoked by atropine is significant only at 20 minutes after the "plateau" period.

Pilocarpine. The small doses of pilocarpine did not modify significantly any of the BPS parameters, except for one period of the rate of flow (Figs. 2–4). The series of high doses evoked modifications on the rate of flow more marked than the small doses (Fig. 2); on the other BPS parameters it elicited a significant depression of just one period of bicarbonate output (Figs. 2–4).

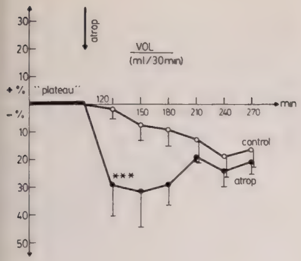
Atropine plus pilocarpine. Graded doses of pilocarpine superimposed on the atropine-induced "plateau" produced an excitation of BPS parameters, unlike pilocarpine alone. This discrepancy between percentage changes in both series is evident in all the secretory parameters (Figs. 10–12).

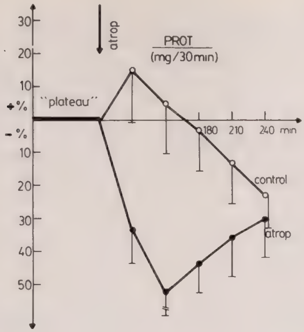
Vagotomy and Vagotomy plus Pilocarpine. The spontaneous BPS pattern of rats subjected to truncal vagotomy differs from that of control animals (Figs. 13–15). Superimposing graded doses of pilocarpine on the "plateau" stage of vagotomized animals reestablishes the normal BPS pattern. This is clearly seen with bicarbonate and protein output (Figs. 14, 15). Rate of flow changes (Fig. 13) elicited by pilocarpine on vagotomized animals seem to disclose the hypersensitivity of the cholinergic-dependent inhibitory mechanism (PP?) that normally modulates BPS.

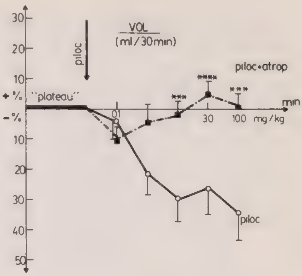
Chronic Alcoholism. In the rats fed alcohol for 6 months, the spontaneous BPS percentage changes in respect to the "plateau" stage did not differ significantly from changes observed in the control group (Figs. 16–18).

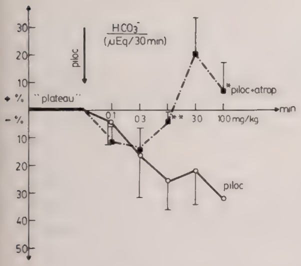
In another series of 6-month alcohol-treated animals, pilocarpine given in graded doses did not induce BPS percentage changes in respect to the "plateau" different from those obtained in the control rats either with or without superimposed pilocarpine (Figs. 16–18).

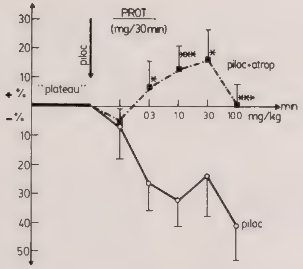
In the rats fed alcohol for 3 months and 18 months, pilocarpine superimposed on an atropine-evoked "plateau" did not evoke, as was observed in nonalcoholic animals, an increase of flow rate (Fig. 19). Concerning protein output, the 3-month alcohol-treated rats behaved similarly to the control animals, but in the 18-month ethanol-fed animals this parameter did not rise after the











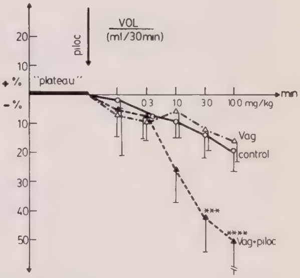


Fig. 8. Top left Volume of EPS. Atropine (0.3 mg/kg) was given intraperitoneally (n:5). Evaluation for 180 minutes of percentage changes in respect to "plateau" levels as compared with the same periods of spontaneous modification observed in controls (n:17). *** $p < 0.01$. Key as in Fig. 2.

Fig. 9. Top center Protein output of EPS. Spontaneous and atropine-induced percentage changes in respect to "plateau" levels. Key in Fig. 2.

Fig. 10. Top right Volume of EPS. Analysis of percentage changes elicited by increased doses of pilocarpine in control animals (n:7) and atropine pretreated (piloc + atrop; n:15). *** $p < 0.01$; **** $p < 0.001$. Key as in Fig. 2.

Fig. 11. Bottom left Bicarbonate output of EPS. Pilocarpine-induced changes (in percent) in respect to "plateau" levels in controls with and without atropine. * $p < 0.05$; ** $p < 0.02$. Key as in Fig. 2.

Fig. 12. Bottom center Protein output of EPS. Pilocarpine-induced percentage changes in respect to "plateau" levels in controls with and without atropine. * $p < 0.05$; *** $p < 0.01$. Key as in Fig. 2.

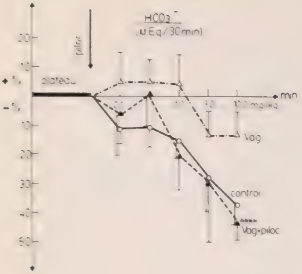
Fig. 13. Bottom right Volume of EPS. Spontaneous and pilocarpine-induced percentage changes in respect to "plateau" levels in controls (n:17) and chronic truncal vagotomized rats (n:11). *** $p < 0.01$; **** $p < 0.001$ compared with pilocarpine (n:8) and without pilocarpine in vagotomized rats. Key as in Fig. 2.

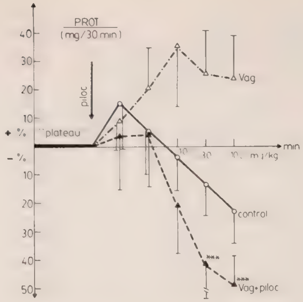
cholinomimetic except with the highest dose. (Fig. 20).

Discussion

The results of the present experiments show that graded doses of pilocarpine, primarily the series of high doses, either inhibit or do not modify the "plateau" values of the diverted, no-recirculated BPS. The cholinomimetic-elicited percentage drop of BPS is significant for volume and bicarbonate output (Figs. 2, 3) and not significant for protein output (Fig. 4).

Blocking of the muscarinic receptors with atropine given intraperitoneally on the "plateau" stage evoked, in control animals, a significant depression of both hydrelatic and ecbolic BPS parameters (Figs. 5–7). As shown for flow rate and HCO_3^- output (Figs. 8, 9), the atropine-induced percentage depression in respect to the "plateau" level is well sustained for 150 minutes.





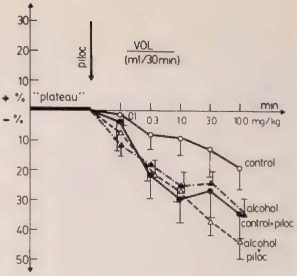


Fig. 14. **Left** Bicarbonate output of EPS. Spontaneous and pilocarpine-induced percentage changes in respect to "plateau" levels in controls and chronic truncal vagotomized rats. **** $p < 0.001$ in vagotomized rats with or without pilocarpine. Key as in Fig. 2.

Fig. 15. **Center** Protein output of EPS. Spontaneous and pilocarpine-induced percentage changes in respect to "plateau" levels in controls and chronic truncal vagotomized rats. *** $p < 0.01$. Key as in Fig. 2.

Fig. 16. **Right** Volume of EPS. Spontaneous and pilocarpine-induced percentage changes in respect to "plateau" levels in normal (controls, n:17); control plus pilocarpine (n:7) and 6-month alcohol-fed rats (alcohol, n:8); alcohol plus pilocarpine, (n:7). Key as in Fig. 2.

When pilocarpine, in graded doses, is superimposed on an atropine-induced BPS "plateau," a reversal phenomenon is observed. Indeed, flow rate as well as bicarbonate and protein output show a significant percentage increase when compared with the respective periods in the series of pilocarpine without atropine. The increase grows larger as the dose of pilocarpine increases (Figs. 10–12).

To explain the lack of change or the depression of the BPS "plateau" values induced by the graded doses of pilocarpine, two alternatives seem plausible. The first one is that of supramaximal inhibition. This concept centers on the assumption that during the BPS "plateau" stage the intrapancreatic cholinergic tone is at maximum. This would be primarily the result of an increased firing of nervous impulses through the duodenopancreatic reflexes triggered by the intraduodenal absence of BPS. The basis of the phenomenon of supramaximal inhibition is the destructive effect of supraoptimal concentration of the secretagog on the target cells. Adler et al (10) have shown, in rats, that supraoptimal stimulation of the pancreas with carbacohol induces an injury in the Golgi region starting with vacuolation of the cytoplasm. In addition, lysosomes are activated and cellular organelles and secretion granules are destroyed.

The second alternative that could explain the effects of pilocarpine in the present series of experiments is that the cholinomimetic releases, at pancreas level, through an indirectly cholinergic pathway an inhibitory regulatory peptide and/or another factor: pancreatic peptide (PP), somatostatin, enkephalin, substance P, serotonin, prostacyclin, ACTH, thyrotropin-releasing hormone. In this line of reasoning a relevant recent observation is that in humans graded doses of urecholine given intravenously do not change enzyme secretion and do not modify plasma levels of PP and somatostatin (11). This unexpected lack of effect by the cholinominetic is prostaglandin-dependent. Indeed, when the tests were repeated (previous indomethacin treatment) they revealed an increase of the pancreatic enzyme secretion. This implies that one kind of prostaglandin has an inhibitory influence on exocrine pancreatic secretion (EPS). This was confirmed by Konturek et al (12) showing that prostacyclin elicits an inhibitory effect on EPS stimulated either endogenously (test meal) or intravenously (secretin).

An interesting observation that gives support to this second alternative is that in vagotomized animals, graded doses of pilocarpine return the altered BPS secretory pattern to normal (Figs. 13–15), which seems to imply that the cholinomimetic in these animals acting via the activation of cholinergic receptors reestablishes the influence of a factor and/or regulatory peptide (PP? prostacyclin? somatostatin? enkephalins?) which normally modulates BPS and is lost after section of the vagal nerves.

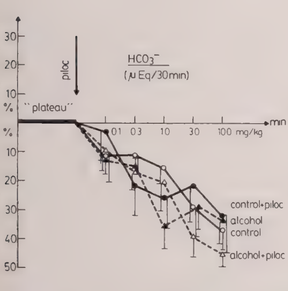
Concerning the BPS reversal changes when pilocarpine is superimposed on an atropine-evoked BPS "plateau" (Figs. 10–12), we surmise that this is the consequence of the activation of ganglionic nicotinic receptors with the release at pancreas level of a regulatory peptide with an atropine-resistant excitatory capacity on both the acinar and centroacinar-ductal segments of the "pancreon" (13), but mainly on the latter. One of the regulatory peptides that fulfill these requirements is VIP. Indeed, fitting with the whole picture, VIP is released through the activation of nicotinic receptors, and its effects are atropine-resistant (14, 15).

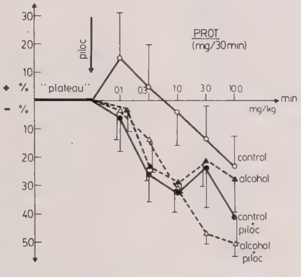
Relevant here is the recent report by Lygren et al (16). In healthy students, they found a significant increase in peripheral plasma VIP when atropine was given together with insulin, whereas insulin or atropine alone had no effect on plasma VIP. They also suggest that cholinergic nicotinic receptors may be involved in the increase of VIP after insulin-induced hypoglycemia and that the lack of VIP increase seen after insulin alone may be caused by an inhibitory effect of other gastrointestinal hormones.

Another report that should be taken into account is that of Lundberg et al (17) in cats. They observed that parasympathetic nerve stimulation caused a maximal vasodilatation and a 500-fold increase in VIP output from the nasal mucosa. Atropine pretreatment, which is known to abolish nasal secretion, caused a further 3-fold increase in VIP output during nerve stimulation. According to these investigators, the increased output of VIP during parasympathetic nerve stimulation by atropine pretreatment suggests that the transmitter acetylcholine may inhibit the release of the coexisting peptide, that is, VIP, via muscarinic autoreceptors.

As for the BPS pilocarpine-induced changes in the alcohol-fed animals, it should be stressed that this cholinomimetic agent, when given alone, does not evoke BPS changes that differ significantly from those observed in the control rats (Figs. 16–18). This at least is what we have observed in animals subjected to a 6-month period of alcohol feeding. Taking into account what we have observed, it would be advisable to repeat this type of test after a more prolonged period of ethanol treatment.

In the atropine-pretreated 3-month and 12-month alcohol-fed animals, pilocarpine was unable to trigger a BPS excitatory flow response as in control animals (Fig. 19). For protein output the changes seem to be correlated with the al-





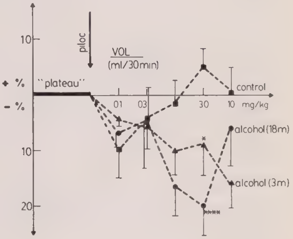


Fig. 17. Left Bicarbonate output of EPS. Spontaneous and pilocarpine-induced percentage changes in respect to "plateau" levels in controls and 6-month alcohol-fed rats. Key as in Fig. 2.

Fig. 18. Center Protein output of EPS. Spontaneous and pilocarpine-induced percentage changes in respect to "plateau" levels in controls and 6-month alcohol-fed rats. Key as in Fig. 2.

Fig. 19. Above right Volume of EPS. Pilocarpine-evoked percentage changes in respect to atropine-induced "plateau" values in controls (n:15) and alcohol-fed rats 3 months (3 m; n:6) and 18 months (18 m; n:6). * $p < 0.05$; **** $p < 0.001$ when compared with controls. Key as in Fig. 2.

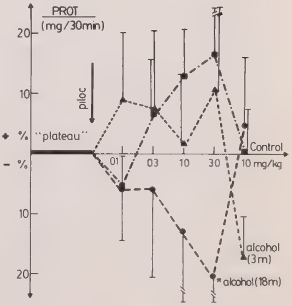


Fig. 20. Right Protein output of EPS. Pilocarpine-evoked percentage changes in respect to atropine-induced "plateau" values in controls and alcohol-fed rats (3 and 18 months). * $p < 0.05$, when compared with controls. Key as in Fig. 2.

cohol feeding time. At 3 months period the percentage modification did not differ from controls, but at 18 months pilocarpine superimposed on atropine-evoked "plateau" did not differ from what was seen with pilocarpine alone (Fig. 20).

We have speculated, similarly to Schmidt et al (1–5) in dogs, that the latter finding may be explained by an alcohol-induced subsensitivity of the nicotinic ganglionic receptors through which pass the flow of impulses in the cholinergic nerves to or in the pancreas. The consequence would be a decreased release of a regulatory peptide, mediated by nicotinic receptors, with an atropine-resistant excitosecretory capacity on the "pancreon" units. This again points out the probable involvement of VIP and perhaps of other peptides or factors with the same capacity.

Concerning the intrinsic mechanism responsible for the ethanol-induced ganglionic nicotinic subsensitivity, we speculate—similarly to our prior line of reasoning to explain the elevated intrapancreatic cholinergic tone (18–26) and the subsensitivity of the muscarinic receptors (20–23, 27)—that this is the result of a previous stage of an alcohol-elicited increase in traffic of nervous impulses.

The present observations give further insight into the understanding of the intrinsic mechanisms that mediate the physiopathogenic changes elicited by chronic alcoholism in the pancreatic gland. Indeed, in our view, supported by physiological observations in sympathetic and parasympathetic ganglia (28), the ethanol-evoked impairment of the ganglionic nicotinic receptors elicits an imbalance in the transmission of nervous impulses, triggering a prevalence of the nonnicotinic pathway. This is precisely the route activated by CCK-PZ, gastrin (29), serotonin (30), and probably ethanol itself (28, 31–35), a route which releases acetylcholine at postganglionic endings.

Speculating even further, we think that the ethanol-evoked impairment of the ganglionic nicotinic receptors is, in some way, the pivotal factor around which revolves the increased "pancreon" ecbolic response after intraduodenal stimuli (18, 36) and intravenous CCK-PZ (31). Indeed, it has been shown in dogs that after a few weeks of alcohol feeding there is a remarkable augmentation of the "pancreon" ecbolic and hydrelatic response to intravenous CCK-PZ stimulation (31). In respect to the nonalcoholic period the difference is about 100% for protein, 34% for rate of flow, and 47% for bicarbonate output. The same happens when one compares pancreatic protein output elicited by an intraduodenal oleic acid infusion in nonalcoholic and alcohol-fed dogs (18, 36). These findings were confirmed in humans by collecting, by Wirsung catheterization, pure pancreatic juice and comparing the EPS to bolus injections of secretin and CCK-PZ in controls and chronic alcoholic subjects (37).

Another physiologic observation coherent with this hypothesis is that in dogs submitted to a continuous perfusion of secretin plus CCK-PZ, an anesthetic agent (Lidocaine) that blocks preferentially ganglionic nicotinic receptors, when given either topically on the Vaterian region or by intravenous injection, triggers a percentage increase over the "plateau" stage that is significantly greater in alcohol-fed animals than in controls and that is augmented by atropine pretreatment (38).

A notion to be stressed is that the dog's plasma levels of CCK-PZ measured by a biological method remain unchanged during the alcohol-fed stage (39). Another observation to emphasize is that atropine pretreatment diminishes the EPS response to intraduodenal oleic acid infusion and suppresses the ecbolic EPS differences between nonalcoholic and alcohol-fed animals (40).

In order to fully grasp the implications of this last finding we should be aware of Grossman's hypothesis (41): CCK-PZ secreted by intraduodenal stimuli (small loads of fats and aminoacids) induces a "pancreon" ecbolic response, activating a nervous reflex at the duodenopancreatic level through a paracrine-neural mechanism and releasing acetylcholine at postganglionic endings (Fig. 21 A, B). A peculiar capacity of CCK-PZ is that of activating other neurones evoking arc reflexes. From the duodenum it would trigger to the pancreas, and to the rest of the gastrointestinal tract, long (vago-vagal), medium (integrated in the celiac ganglion), and short (duodeno-pancreatic) reflexes. These are the basis, for example, of the satiety effect of CCK-PZ. This has been well proven in animals and humans and there are many indications that the intrinsic mechanism is the activation of the afferent fibers in the vagus (42). CCK-PZ also inhibits gastric emptying.

It is suggestive that these physiologic events are blocked by abdominal vagotomy (42). In esophagus, CCK-PZ elicits the relaxation of the lower esophageal sphincter through the mediation of VIP (43, 44). In the colon, a fat meal releasing CCK-PZ evokes increased motility (45, 46) through an arc reflex, probably integrated in the celiac plexus (47, 48), that activates opiate neurones in the myenteric plexus of the gut (46).

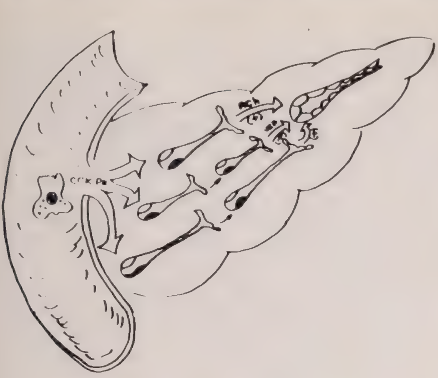


Fig. 21A. Left Schematic drawing of paracrine-neural mechanism triggered by CCK-PZ at duodenopancreatic level, positive component. Peptide activates ganglionic nonnicotinic pathway releasing Ach which acts directly on the "pancreon" units, elicits a cascade of events resulting from activation of other neurones.

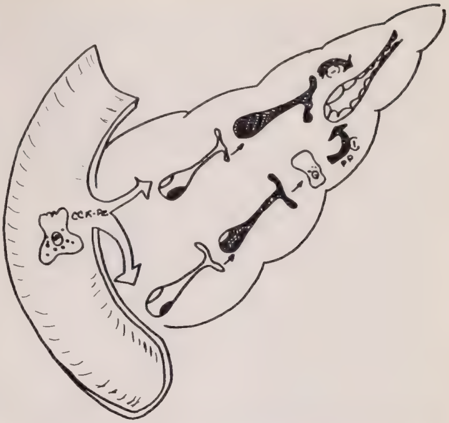


Fig. 21B. Right Schematic drawing of negative component of interplay on the "pancreon" units elicited by CCK-PZ. Pancreatic polypeptide (PP) released from endocrine cells in pancreas is probably mainly responsible.

In the human and cat sphincter of Oddi, CCK-PZ produces a decrease in resistance to flow (49). This effect is due to the stimulation of nonadrenergic, noncholinergic inhibitory nerves (VIP?). This neural inhibitory action, similar to what happens in the esophagus, overrides a direct stimulatory effect on smooth muscle.

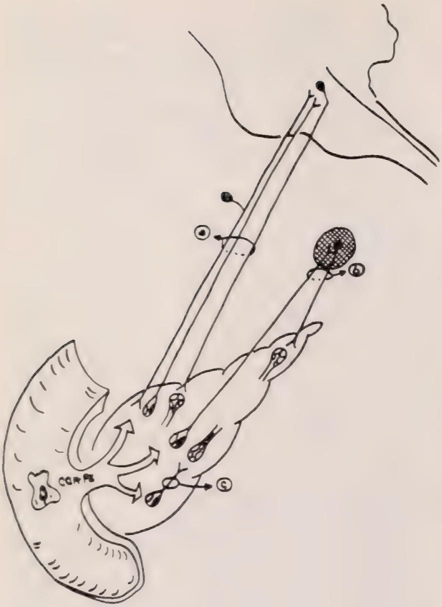
We hypothesize that from the duodenum, CCK-PZ released through the paracrine-neural modality elicits two interplaying mechanisms, one excitatory and the other inhibitory (Fig. 21 A, B).

The excitatory mechanism (Fig. 21A) might be related to the release of acetylcholine alone and activation of muscarinic receptors on the "pancreon" cells by means of short, medium, and long arc reflexes (Fig. 22). Additionally, there could be a cascade of events elicited by acetylcholine released through the nonnicotinic pathway. Among them one should consider a regulatory peptide with a bombesin-like capacity and prostaglandins of the type E with an ecbolic effect (51).

The inhibitory mechanism (Fig. 21B) might be related to the CCK-PZ activation of several factors and/or peptides, presumably also via the same short, medium, and long arc reflexes (Fig. 22). Pancreatic polypeptide (PP) undoubtedly is involved (52–54), and presumably one might consider the participation of somatostatin (55), prostacyclin (12), enkephalins (56), substance P (57), serotonin (58), adrenocorticotropic hormone (ACTH) (59) and thyrotropin-releasing hormone (60) (Fig. 21B).

When greater amounts of CCK-PZ are released by large intraduodenal loads of fats and aminoacids, the plasma circulating CCK-PZ, besides acting directly on the "pancreon" receptors, might trigger at the intrapancreatic ganglia the same interplay of excitatory and inhibitory impulses as discussed above.

Besides CCK-PZ, ethanol would, like the scorpion toxin (50), be able to activate the ganglionic nonnicotinic pathway releasing acetylcholine at nerve endings. This is inferred from the following facts: first, in dogs, Maitrya (61) concluded that alcohol acted as a gastric secretagogue stimulating the myenteric plexus and the hypothalamic bulbar centers following absorption. Both mechanisms are abolished by atropine. Second, the alcohol stimulation of gastric pouches is potentiated after vagotomy (62). Note that vagal decentralization enhances peripheral neural transmission through the ganglionic nonnicotinic pathway (28). Third, in humans (63), atropine, but not hexamethonium, given either before or after the standard dose of alcohol (20 ml intravenously), almost completely inhibits its gastric stimulatory action. Fourth, in dogs, atropine but not hexamethonium prevents the excitatory effect on secretin-induced EPS, a phenomenon also observed in vagotomized animals (33). Also, in alcohol-fed rats subjected to truncal vagotomy, BPS protein values are higher than in those animals either vagotomized or ethanol-treated alone (unpublished observations). Therefore, in



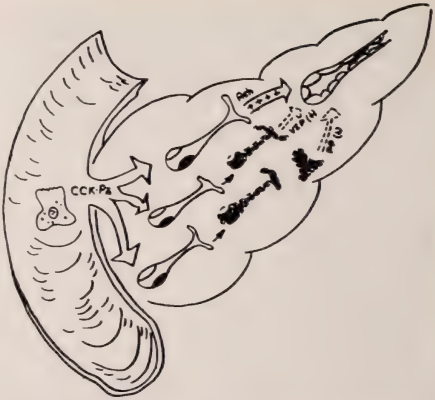


Fig. 22. Left Schematic representation of long (vago-vagal) (a), medium (integrated in the celiac ganglia) (b), and short (duodenopancreatic) (c) reflexes elicited by CCK-PZ at duodenal level.

Fig. 23. Right Schematic drawing of ethanol-induced subsensitivity of ganglionic nicotinic receptors.

humans and in animals accustomed to chronic alcohol consumption, in contrast to nonalcoholics, ethanol acts at the periphery, either on muscarinic receptors of the intrapancreatic ganglion cell (deutoneuron of the vagus nerve), and/or directly on the muscarinic receptor of the acinar cell itself (35).

From the foregoing considerations evolves, by logical inference, the potential danger to the pancreas of associating chronic alcohol ingestion with foods that are well-known releasers of CCK-PZ, such as protein and fats. A supporting observation is the Sarles school finding (64–66) of a significant association between alcoholic pancreatitis (but not hepatic cirrhosis) and a hyperproteic and hyperlipidic diet.

Another important physiological observation is that VIP (67) has a potentiating effect, increasing the affinity but not the numbers of Ach receptors. VIP would switch muscarinic receptors to high-affinity conformer and thereby augment their efficiency in changing Na^+ permeability and secretion. Hedlung et al (68) emphasize that a possible molecular mechanism for the synergistic actions of Ach and VIP is the 10,000-fold increase induced by VIP in the affinity of Ach for muscarinic receptors. As can be inferred from the present experiments, the alcohol-induced depression of VIP secretion could be at least in part responsible for the salivary and pancreatic gland subsensitivity to cholinergic stimulation (20–23, 27), a condition that, unexpectedly, is not associated with changes in the number of cholinergic receptors (unpublished observations) despite the well-proven elevated intrapancreatic cholinergic tone (18–27).

One could conceive that the deficient secretion of VIP that seems to evolve from the present tests in alcohol-fed rats would be in fact a system of protection for the exocrine pancreas against a noxious stimulus such as acute ethanolism which induces protein hypersecretion at least in part through an elevated intrapancreatic cholinergic tone. One could also speculate that the theoretical VIP depression in chronic alcoholism implied by the present tests might explain the discordance between the histopathologic findings in the rat pancreatic gland and the BPS. Indeed, in unpublished observations, we have found, in alcohol-fed rats, clear signs of ductal and ductular proliferation without a correspondent distinctive increase in the basal rate of flow and bicarbonate output.

In the alcohol-fed stage, besides the discussed enhancement of the ganglionic nonnicotinic pathway activated by CCK-PZ, there would be decreasing influence of this same peptide on the triggering of the inhibitory component that is part of the normal interplay of influences on the "pancreon" units (1–5, 30–35, 65, 66, 69, 71) (Fig. 23). Within the latter, pancreatic polypeptide (PP) plays perhaps the main role. Its release from the endocrine cells, virtually all localized in the pancreatic gland, is mediated through a cholinergic mechanism. This allows us to explain the physiologic observation of Henriksen in dogs (72) in the sense that atropine enhances the rate of flow and bicarbonate output of CCK-PZ-induced EPS. The same happens with truncal vagotomy (73, 74). It is also interesting that an intravenous lidocaine infusion induces a greater percentage increase of a secretin-evoked EPS "plateau" in alcohol-fed that in nonalcoholic dogs (18, 37, 38), a phenomenon enhanced when the same protocol is carried out in atropine-pretreated animals. We have speculated that the intravenous anesthetic agent, by preferentially blocking the ganglionic nicotinic receptors, enhances the nonnicotinic pathway activated by the intravenously perfused CCK-PZ, and that atropine, by blocking the muscarinic receptors, depresses the CCK-PZ-evoked release of PP (38).

One cannot disregard the probable involvement of inhibitory regulatory peptides or factors other than PP, such as somatostatin, enkephalins, prostacyclin, serotonin, ACTH, TRH.

The ethanol-induced vagal neuropathy (75, 76) must also be taken into consideration when analyzing the alteration of the normal interplay of excitatory and inhibitory influences on the "pancreon" units. Indeed, on the one hand this lesion may induce decentralization of the "intermediate autonomic brains," "antral," "duodenal," and "celiac" (18), that favors the excitatory component due to the facilitated transmission of the nervous impulses via the ganglionic nonnicotinic pathway (CCK-PZ and ethanol itself), and on the other through the predominant alteration of the inhibitory fibers (PP, somatostatin, enkephalins) it might impair the "brake" on the "pancreon" cells contributing to complete the imbalance and in this way to trigger the development of what we have called "supranormal ecbolic stimulation" (18).

The ethanol-induced lesion of some of the vagus fibers (75, 76), probably the thinnest one, might also contribute to the impairment of the CCK-PZ elicited release of PP (1–5, 52, 54). The secretion of this regulatory peptide, either alone or associated with other components of the "pancreon brake," may in our view be the result of the activation by CCK-PZ of long (vago-vagal), medium (integrated in the celiac plexus), and short (duodeno-pancreatic) arc reflexes (77) (Fig. 21B, 22). It should be stressed that the same ethanol-evoked imbalance that favors positive versus negative influences on the "pancreon" units develops in chronic renal failure in humans (78, 79). Indeed, in this clinical condition there is an increased EPS response (trypsin) and duodenal contraction rate following a CCK-PZ intravenous infusion and an intraduodenal mannitol perfusion (78). It is a suggestive coincidence that in chronic renal failure there is a high prevalence of pancreatic disease (79).

Clinical Applications. The foregoing physiological analysis does have probable clinical application. In chronic alcoholic pancreatitis patients, mainly in those with frequent acute relapses, it would be logical, besides suppressing alcohol intake, either to surgically shunt the antroduodenal zone (80–83) or to pharmacologically diminish the bombardment of the "pancreon" units by the duodenopancreatic reflexes (18, 83). In acute episodes, some justified therapeutic measures would include nasogastric suction, parenteral alimentation, muscarinic receptors blockers, CCK-PZ antagonists, depression of the hyperactivity of the "antral" and "duodenal" autonomic brains by local anesthetic agents. This approach has been partly tried, but on the whole it still awaits therapeutic evaluation.

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Trophic, Biochemical and Functional Changes in Submaxillary Glands and Pancreas Induced by Chronic Alcohol Feeding as Indirect Effect Mediated by Parasympathetic Autonomic Centers

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Abstract

Chronic ethanol intoxication was induced in rats of both sexes by giving them alcohol as the only source of liquid for 12 weeks. In female rats, unilateral parasympathetic decentralization (section of the chordalingual nerve) was performed either at the beginning of ethanol feeding or three weeks before the end of the alcohol-fed stage. Male rats were subjected to truncal vagotomy plus piloroplasty, and/or celiac ganglionectomy. These procedures were immediately followed by alcohol treatment.

In the submaxillary gland, both alcohol feeding and parasympathetic decentralization induced atrophy. In the pancreas, alcohol prevented the remarkable hypertrophy of the body-tail segment of the gland elicited by chronic vagotomy, but after celiac ganglionectomy alcohol increased the weight of the head.

In the submaxillary gland, activity of choline acetylase (ChAc) was markedly increased after ethanol treatment. This was prevented by parasympathetic decentralization. Moreover, the subsensitivity to methacholine in alcohol-treated rats was reversed when the chordalingual nerve was sectioned. The enhancement in the total activity of ChAc in the head of the pancreas observed after alcohol was prevented by simultaneous vagotomy. No such effects occurred in the body-tail segment of the gland. Celiac ganglionectomy significantly reduced enzyme activity only in the head, and partially prevented the effects of alcohol in both the head and the body-tail segments of the gland. Chronic alcoholism induced increased bicarbonate output, which was prevented by truncal vagotomy but not by celiac ganglionectomy. On the contrary, chronic vagotomy abolished the inhibitory effects on protein output evoked by alcohol. Celiac ganglionectomy by itself triggered an excitatory protein secretion and prevented the inhibitory effects induced by alcoholism. As in both peripheral organs, ChAc activity was significantly increased in the medulla. These results strongly suggest that action of alcohol on peripheral cholinergic-innervated organs is related to the integrity of the different parasympathetic pathways responsible for the trophic, biochemical, and functional control of the organs.

Recent evidence shows that chronic ethanol feeding enhances the cholinergic and/or adrenergic tone in peripheral autonomic-innervated organs (1–5). Trophic, biochemical, and functional studies have suggested that the main mechanism by which chronic ethanol intoxication exerted these modifications on peripheral autonomic organs was through influences on both parasym-

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pathetic and sympathetic centers (1), resulting in increases in the activity of peripheral nerves regulating effectors.

The present experiments were designed to investigate the effects of chronic ethanol treatment on parasympathetically decentralized structures. For this purpose two organs were chosen, the submaxillary and pancreatic glands of the rat, since both are known to be richly dependent on cholinergic innervation for their trophic and secretory activities (6–11).

Material and Methods

Experiments on submaxillary glands were performed on female Wistar rats (initial body weight, 200–230 gm). Pancreas studies were carried out on male rats of the same strain (initial body weight, 290–340 gm). Animals of both sexes were divided into two series, a control group and an experimental group. All rats received a balanced diet of Purina pellets, and water was given ad libitum. In experiments with alcohol, this agent was added to the tap water.

Submaxillary Gland Trophic Studies: Surgical Procedures. In one series of experiments, the wet weights of control and unilaterally parasympathetic and/or sympathetic decentralized glands were determined three months after these surgical procedures had been performed. In other series, ethanol was either given alone or superimposed on surgically decentralized glands. These ethanol studies were carried out in two different ways: (a) ethanol treatment was started the same day surgical procedures were performed; (b) surgical procedures were carried out 21 days before the end of the ethanol treatment. A unilateral parasympathetic decentralization was achieved by section of the chordalingual nerve; unilateral sympathetic decentralization by section of the preganglionic fibers. Both procedures were performed under ether anaesthesia. At the end of the experimental period, submaxillary glands were dissected and carefully cleaned, dried off and weighed (wet weight). To obtain dry weight, glands were dried at 105–110°C for 48 hours. Another evaluation of the changes in glandular wet and dry weight (acetone powder) was obtained when studies on choline acetylase activity were performed on the different experimental groups.

Submaxillary Secretory Responses. To estimate the glands' secretory responses, we anaesthetized rats from the different experimental groups intravenously with chloralose (100 mg/kg) after ether induction. After the trachea was intubated, the ducts of both submaxillary glands were exposed and cannulated with fine glass cannulae that delivered 80 drops from 1 ml of distilled water (12). Dose response curves to methacholine chloride were determined by the sequential injection of 0.03, 0.1, 0.3, 1.0, 3.0 and 10.0 μg/kg of the drug.

Pancreas: Trophic Studies. Changes in the wet weight of the pancreas and of the two segments (head and body-tail) were assessed after the following surgical procedures: chronic truncal vagotomy plus pyloroplasty and/or celiac ganglionectomy. These operations were performed both on controls and on chronically ethanol-treated rats. Two indexes were evaluated: the ratio of gland weight (gm) to body weight (kg); and the ratio of body-tail to head (mg). Chronic truncal vagotomy was performed as previously described (13); celiac ganglionectomy was done by extirpation of this structure located in the mesentery between the celiac artery trunk and the superior mesenteric artery. This artery and the segment of the aorta between the origin of these two trunks were stripped. All surgical procedures were performed under ether anaesthesia.

Pancreas: Secretory Studies. Fistulas were carried out as previously described (13). We collected basal bile-pancreatic secretion from conscious control and ethanol-fed rats restrained in Bollman cages 24 hours after the fistulas. The three collection periods were 30 min each. We considered the average values of the last two periods as the "plateau." The parameters analyzed were (a) bicarbonate concentration (HCO_3^- in mEq/1), determined by the titrimetric method described by Lehmann et al (14) and expressed as HCO_3^- output (in μEq/30 min); and (b) protein concentration, measured according to the method described by Gornall et al (15) and expressed as protein output (mg/30 min).

Choline Acetylase Activity. Enzyme activity was determined in an acetone-dried powder of submaxillary glands, pancreatic glands, and medulla (16) by the method of McCaman and Hunt (17). Enzyme activity was calculated on the basis of the known activity of ^{14}C-Acetyl-CoA and expressed in μg of acetylcholine formed/hr/gland (total activity) or in μg of acetylcholine formed/hr/gm acetone powder (concentration) (18).

Acetylcholinesterase Assay in the medulla was performed using acetyltiocholine as substrate, as reported by Ellman et al (19).

Alcohol Treatment. Rats of both sexes were separated into experimental (alcohol-fed) and control animals. The animals of the experimental group were allowed to drink only a solution of ethyl alcohol according to the following schedule: first week, a 5% solution (v/v); the next two weeks, 10% (v/v); the fourth week, 15% (v/v); the fifth week, the dose increased to 25% (v/v) until on the 90th day, the animals received a solution of 32% (v/v).

Statistical Analysis. The mean and standard error of the results were calculated. The significance between means was evaluated using Student's *t* test for paired and nonpaired values (20). P values less than 5% ($p < 0.05$) were interpreted as significant.

Results

Trophic Studies

Body Weight. The body weight of rats treated with alcohol was found to be 10% lower ($p < 0.05$) than in controls, in both females and male rats.

Submaxillary Glands. The wet weight reduction induced by chronic parasympathetic decentralization (PSD) was about 35%; Controls averaged 187.8 ± 12.2 mg; PSD rats, 122.1 ± 8.6 mg (Fig. 1). Sympathetic decentralization (SD) reduced gland weight by nearly 10% when both procedures were combined, the decrease in gland weight obtained was close to that observed in PSD-only glands (34%: controls, 139.8 ± 7.4 mg; PSD + SD, 92.9 ± 6.5 mg). Chronic alcohol treatment by itself reduced glandular wet weight by nearly 24%, but it did not further reduce glandular wet weight of chronically decentralized parasympathetic or of PSD + SD glands. The wet and dry weight of submaxillary glands, when PSD was carried out 21 days before completion of the alcohol-fed stage, are shown (Table 1).

Pancreas. As previously reported (3, 4, 13), three months after truncal vagotomy, the wet weight of the whole pancreas increased by 81% (Table 2 [B]; $p < 0.001$). This trophic effect is mainly due to an increase of the body-tail segment of the gland (119%). The head weight increased very slightly without reaching statistically significant levels. These findings are reflected whether both indexes (gm/kg) or only the ratio body-tail to head are considered. Both ratios were found to increase in vaguectomized rats by about 70% over control values. Chronic alcohol treatment alone did not induce trophic changes in the gland.

However, chronic ethanol administration to vaguectomized animals not only abolished the hypertrophy induced by vagal decentralization, but elicited a statistically significative reduction (about 20%) in the ratio gm/kg (from 3.01 ± 0.09 in controls to 2.44 ± 0.13 in surgical decentralized and alcohol-treated animals; $p < 0.01$).

Chronic celiac ganglionectomy alone did not evoke trophic changes of the pancreas. In contrast to the previous series, chronic alcoholism provoked an increase in gland weight, mainly of the head (28%; $p < 0.01$). This is reflected in a similar increase obtained in the ratio gm/kg ($p < 0.02$). When both vagotomy and celiac ganglionectomy were performed together, ganglionectomy was found to induce a partial blocking of the trophic changes induced by vagotomy. The increase in the body-tail segment was only 44% over controls, and the gm/kg ratio increased by only about 23% and was statistically significant ($p < 0.01$). Chronic ethanol administration did not modify the weight of the glands that underwent both vagotomy and celiac ganglionectomy (Table 2).

Choline Acetylase Activity

Submaxillary Glands. The total activity as well as the concentration of choline acetylase (ChAc) in the submaxillary glands of ethanol-treated rats were 40% greater than the enzyme activity found in controls ($p < 0.001$) (Figs. 2–4).

Total enzyme activity markedly decreased—by 42%—within three months after PSD (from 13.5

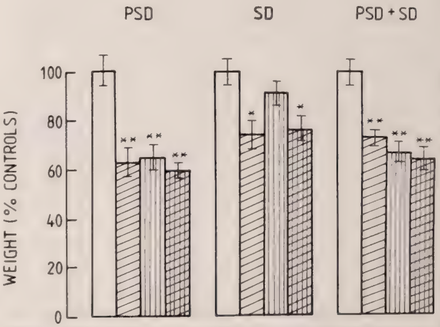


Fig. 1. Wet weight of submaxillary glands of rat after chordalingual section (PSD); sympathetic decentralization (SD); and parasympathetic + sympathetic decentralization (PSD + SD) in normal (unruled column) and alcohol-fed (diagonal rule) rats. Ordinate: wet weight in % of controls. Left: PSD (vertical rule); PSD + alcohol (diagonal plus vertical rule). Center: SD (vertical rule) SD + alcohol (diagonal plus vertical rule). Right: PSD + SD (vertical rule); PSD + SD + alcohol (diagonal plus vertical rule). Values are means ± SEM of at least 12 experiments per group.
*$p < 0.02$; **$p < 0.001$.

TABLE 1

Body Weights and Weights of Submaxillary Glands of Control (Contralateral Innervated) and Ethanol-Fed PSD Rats

	Body Weight (gm)	Submaxillary glands (mg)			
		Innervated		PSD	
		Wet	Dry	Wet	Dry
Control (n = 11)	258.5 ± 7.92	163.7 ± 12.16	46.2 ± 2.03	125.8 ± 9.70	32.6 ± 1.48
Ethanol (n = 12)	234.6 ± 6.35*	119.5 ± 15.61‡	36.5 ± 1.67‡	113.2 ± 8.20	31.9 ± 2.06
Ethanol control percentage	90.6 ± 1.14†	73.0 ± 6.0‡	79.0 ± 6.3‡	89.9 ± 7.0	97.9 ± 4.3

Values are mean ± SEM of *n* experiments.

* $p < 0.05$ compared with controls. †$p < 0.01$ compared with controls. ‡$p < 0.001$ compared with controls.

± 0.50 in controls to 7.8 ± 0.61 μg Ach/gl/h in PSD glands). When enzyme activity was calculated as concentration, PSD glands showed a decrease of 36%. Parasympathetic decentralization totally prevented the increase in enzyme activity evoked by chronic ethanol feeding. Sympathetic decentralization obtained by cutting the preganglionic sympathetic fibers induced a significant increase in enzyme activity, whether expressed as concentration (by about 21%) or as total activity (27%). Sympathetic decentralization did not affect the increased enzyme activity observed in rats treated only with alcohol (Fig. 3).

When PSD and SD were combined, both total activity and enzyme concentration were significantly decreased by 21% over control values (Fig. 4). Thus, enzyme activity showed the same pattern as that observed after PSD only (Fig. 2). In innervated glands, chronic ethanol feeding had increased both total enzyme activity (33%) and enzyme concentration (38%). Yet when ethanol treatment was superimposed on decentralization, its previously excitatory effects on ChAc total activity were prevented to the same degree as that observed after PSD (Figs. 2, 4).

Pancreas. Enzyme activity was determined for both head and body-tail of the pancreas. As previously reported ChAc content varied considerably between these two structures (3, 4, 13). Indeed, in controls the enzyme content of the head was significantly higher (by about 50%) than that of the body-tail. Thus, the average concentration

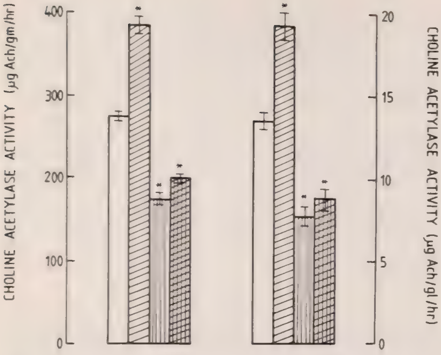
TABLE 2

Body Weights and Weight of Pancreas of Controls and Alcohol-Fed Rats Subjected to Chronic Truncal Vagotomy plus Pyloroplasty, and Celiac Ganglionectomy (CG)

Groups	Body weight (gm)	Pancreas (mg)			Gland: body weight (gm/kg)	Ratio body + tail: head (gm/gm)
		Whole	Head	Body + tail		
Control (A) (n = 20)	352 ± 7.87	1054 ± 31.9	445 ± 24.7	604 ± 27.2	3.01 ± 0.09	1.44 ± 0.12
Control (B) (n = 20)	444 ± 6.28	1270 ± 36.2	533 ± 21.8	745 ± 29.0	2.87 ± 0.09	1.45 ± 0.09
Alcohol (A) (n = 15)	417 ± 18.89	1288 ± 73.6	531 ± 30.5	732 ± 56.5	3.22 ± 0.22	1.37 ± 0.06
Vagotomy (A) (n = 15)	391 ± 15.52	1911 ± 115.5§	604 ± 69.0	1322 ± 119.0§	5.0 ± 0.32§	2.49 ± 0.32‡
Vagotomy + alcohol (A) (n = 8)	379 ± 19.45	921 ± 66.5	377 ± 36.9	544 ± 48.3	2.44 ± 0.13‡	1.51 ± 0.18
CG (B) (n = 23)	436 ± 16.40	1309 ± 71.2	578 ± 24.2	732 ± 58.2	3.09 ± 0.19	1.28 ± 0.10
Alcohol + CG (B) (n = 13)	444 ± 16.5	1576 ± 173.0*	682 ± 47.8‡	894 ± 139.7	3.59 ± 0.33†	1.30 ± 0.12
Vagotomy + CG (A) (n = 15)	384 ± 14.64	1420 ± 93.3§	548 ± 36.1†	872 ± 72.6	3.71 ± 0.23‡	1.62 ± 0.12
Alcohol + Vagotomy + CG (B) (n = 5)	373 ± 20.17	1333 ± 78.6	560 ± 44.4*	773 ± 42.1‡	3.57 ± 0.25*	1.40 ± 0.08

Values are means ± SEM of n experiments.

* $p < 0.05$ compared with controls (A) and (B). †$p < 0.02$ compared with controls (A) and (B). ‡$p < 0.01$ compared with controls (A) and (B). §$p < 0.001$ compared with controls (A) and (B).



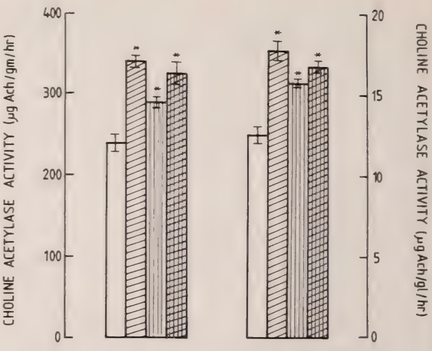


Fig. 2. **Top left** Choline acetylase activity in submaxillary glands of controls (unruled column); ethanol-treated (diagonal rule); PSD (vertical rule); PSD + ethanol treated rats (diagonal plus vertical rule). Right, enzyme activity in µg Ach/gl hr (total activity); left, enzyme activity in µg Ach/gm/hr (concentration). Values shown are means ± SEM of at least 12 experiments.
$^*p < 0.001$ when compared with control values.

Fig. 3. **Top right** Choline acetylase activity in submaxillary glands of control (unruled column); ethanol treated (diagonal rule); SD (vertical rule); and SD + ethanol-treated rats (diagonal plus vertical rule). Right, enzyme activity in µg Ach/gland/hr (total activity; left, enzyme activity in µg Ach gm/hr (concentration). Values shown are means ± SEM of at least 12 experiments.
$^*p < 0.001$, when compared with control values.

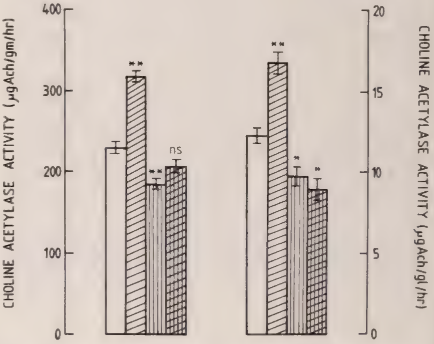


Fig. 4. **Right** Choline acetylase activity in submaxillary glands from control (unruled column); ethanol-treated (diagonal rule); PSD + SD (vertical rule); and (PSD + SD) + ethanol-treated rats (diagonal plus vertical). Right, enzyme activity in µg Ach gland hr (total activity); left, enzyme activity in µg Ach/gm/hr (concentration). Values shown are means ± SEM of at least 12 experiments.
$^*p < 0.01$; $^{**}p < 0.001$ when compared with control values.

of ChAc in the head was 284.9 ± 10.58 µg Ach/gm/hr (n = 8), significantly higher ($p < 0.001$) than that of the body-tail (190.7 ± 3.18 µg Ach/gm/hr). The total ChAc activity, calculated per whole gland, was also significantly different ($p < 0.001$), for example, 17.3 ± 0.59 µg/Ach/gl/hr in the head and 10.9 ± 0.52 µg Ach/gl/hr in the body-tail. When compared with their respective controls (Fig. 5), ChAc activity calculated per whole head or whole body-tail after chronic ethanol treatment was significantly increased in both segments of the gland, by 34% and 28%, respectively. On the other hand, chronic truncal vagotomy induced about a 35% ($p < 0.001$) fall in both total activity and enzyme concentration. Alcohol feeding superimposed on vagotomized rats evoked a reversion in enzyme values that in the head reached control values both when expressed as total activity or calculated as concentration. In the body-tail segment this ethanol-induced reversion on parasympathetically decentralized glands was still higher. Indeed, enzyme concentration and total activity reached levels similar to those obtained after ethanol treatment alone.

Chronic celiac ganglionectomy decreased ChAc activity (Fig. 6). ChAc activity calculated per whole head was 31% less in ganglionectomized animals (12.4 ± 0.8 µg Ach/head/hr) than in controls (8.6 ± 0.7 µg Ach/head/hr). Total activity was also lower in the body-tail segment (10.4 ± 0.8) than in controls (8.3 ± 0.7 µg Ach/body-tail/hr), although this difference did not reach statistically significant levels. When expressed as concentration, enzyme activity depression induced by ganglionectomy was also more marked for the head (nearly 20%) and not significant for the body-tail segment (12%). Alcohol feeding in ganglionectomized animals reversed the changes induced by the surgical procedure, although levels of enzyme activity in the segments studied did not

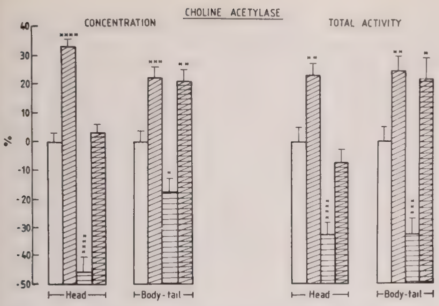


Fig. 5. Choline acetylase activity in head and body-tail of pancreas of control (unruled column); ethanol-treated (diagonal rule); truncal vagotomized (horizontal rule); and vagotomized + ethanol-treated rats (horizontal rule plus diagonal). Ordinate: % changes in enzyme activity in respect to controls. Left, enzyme activity in μg Ach/gm/hr (concentration); right, enzyme activity in μg Ach/head or body-tail/hr (total activity). Values shown are means ± SEM of at least 10 experiments.
*$p < 0.05$; **$p < 0.02$; ***$p < 0.01$; ****$p < 0.001$.

reached the values elicited by alcohol treatment alone.

Secretory Studies

Submaxillary Responses. In control animals, the threshold dose for methacholine was found to be 0.1–0.3 μg/kg. After alcohol treatment, sensitivity to the parasympathomimetic agent was significantly decreased (Fig. 7). Indeed, the threshold dose necessary to elicit a secretory response was ten times higher (3.0 μg/kg). On the other hand, the threshold of the methacholine dose was significantly decreased after parasympathetic decentralization in both controls and alcohol-fed rats. Whether section of the chordalingual nerve was performed simultaneously with the beginning of alcohol treatment or three weeks before completion of ethanol treatment, the secretory response of the decentralized gland to the sialagog agent was increased, as evidenced by the shift to the left of the control curve by nearly 0.6 log units when compared with their respective controls, or when related to the curves obtained in rats fed only ethanol. In the ethanol-only rats, on the other hand, th dose-response curve to methacholine was shifted to the right of that of controls. Furthermore, the maximal secretory response from these glands was markedly reduced (by about 50%). In decentralized glands, the maximal secretory response was significantly increased ($p < 0.001$). In decentralized and alcohol-fed animals, values obtained did not differ from those observed in controls (compare Figs. 7A and 7B).

Basal Pancreatic Activity

Bicarbonate Output. In chronic ethanol-fed rats, bicarbonate output was significantly increased by about 40% over controls ($p < 0.01$). Chronic truncal vagotomy prevented this ethanol-induced increase. On the contrary, celiac ganglionectomy significantly decreased bicarbonate secretion (by about 21%) but did not prevent excitatory changes induced by ethanol feeding (Fig. 8).

Protein Output. Ethanol feeding reduced protein output by about 30% ($p < 0.02$). As previously reported, protein output was not influenced by chronic vagotomy (13), although it prevented the depression evoked by alcohol treatment. On the other hand, chronic celiac ganglionectomy induced a remarkable increase—about 63% ($p < 0.01$)—of protein output. In ganglionectomized rats, ethanol feeding showed a tendency to reduce the augmentation provoked by celiac ganglionectomy alone, although values obtained were still above those obtained by alcohol treatment alone (Fig. 9).

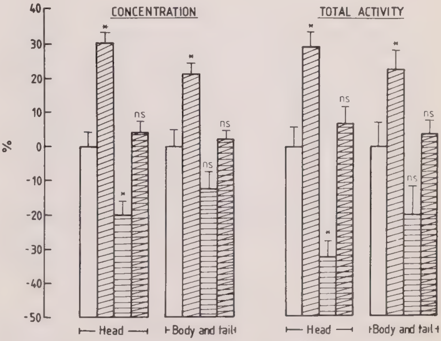


Fig. 6. Choline acetylase activity in head and body-tail of pancreas of control (unruled column); ethanol-treated (diagonal rule); chronic celiac ganglionectomized (horizontal rule); and celiac ganglionectomized + ethanol treated rats (horizontal plus diagonal). Ordinate: % changes in enzyme activity in respect to controls. Left, enzyme activity in μg Ach/gm/hr (concentration); right, ChAc activity in μg Ach/head or body-tail/hr (total activity).
Values shown are means ± SEM of at least 6 experiments.
*$p < 0.001$.

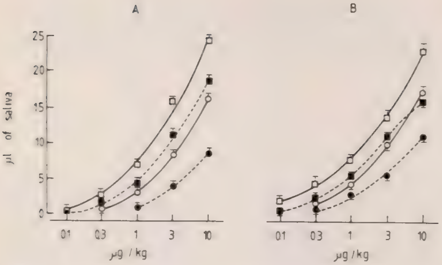


Fig. 7. Dose-response curves to methacholine of submaxillary glands of control (○); alcohol-fed (●); chronic PSD (□); and chronic PSD + alcohol-fed rats (■). A: Chordalingual nerve was sectioned simultaneously with beginning of alcohol treatment; B: parasympathetic nerves were sectioned 21 days before end of alcohol treatment. Ordinate: microliters (µl) of saliva. Abscissa: methacholine in µg/kg. Shown are means ± SEM of at least nine experiments.

Choline Acetylase Activities in Medulla

The concentration of ChAc in the medulla of ethanol-treated rats was significantly increased by nearly 50% when compared with the enzyme activity found in controls (Table 3). On the other hand, the activity of acetylcholinesterase, responsible for the inactivation of the cholinergic neurotransmitter showed a slight decrease (about 14%) in medullas of alcohol-fed rats.

Discussion

Earlier investigations by our group have shown that chronic ethanol ingestion in rats produces hyperactivity of both cholinergic and adrenergic tone in autonomically innervated organs (1–5). Thus, in those organs in which sympathetic innervation has an important function (submaxillary gland, heart, spleen), endogenous norepinephrine levels were higher, and subsensitivity to exogenous neurotransmitter was found (1, 5). On the other hand, in the pancreas, where the sympathetic system does not seem to play an important role, no such changes were observed (1). Yet in the pancreas as well as the submaxillary gland, size, structure, and function are regulated mainly by impulses originating from central parasympathetic neurones (6–8, 13, 16), and chronic ethanol feeding has been found to increase the weight of the pancreas in relation to body weight (13, 21) and to slightly atrophy the submaxillary gland.

However, in both structures, as in other cholinergically innervated organs, the acetylcholine synthesizing enzyme, ChAc, expressed per whole organ or as concentration (1, 2), has been found to be increased. There is experimental evidence that the intensity of traffic of impulses in a nervous pathway alters the transmitter-synthesizing enzymes at the nerve endings in effector organs (22), both when augmented (23–25) and when diminished (3, 4, 13, 26–28) from average conditions. Based on this, the hypothesis was tested that chronic alcohol ingestion might "directly" influence the parasympathetic centers of the central nervous system and increase the flow of impulses in the nerve endings of the effective organs. For this purpose, trophic, biochemical, and functional changes induced by chronic ethanol feeding were analyzed in parasympathetically decentralized submaxillary and pancreatic glands.

As in previous reports, the body weights of chronically alcohol-treated female and male rats were lower than the weights of respective controls (1). Parasympathetic decentralization of either submaxillary glands or pancreas did not modify the body weight of controls or of alcohol-fed rats. Thus, the decrease in body weight induced by alcohol consumption may be attributed either to decreased food intake or to a specific action of alcohol ingestion. Nevertheless, whatever the mechanism by which ethanol impairs the rate of body weight increase, it is striking that the rate

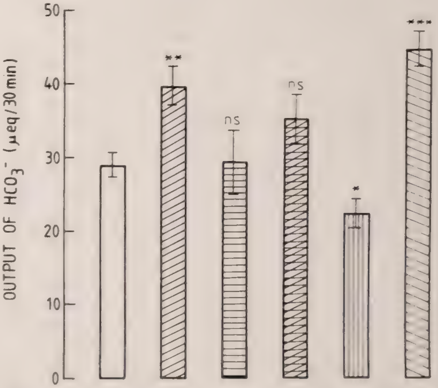


Fig. 8. Bicarbonate output of bile-pancreatic juice from control (blank square); chronic ethanol-fed (diagonal rule); chronic vagotomized (horizontal rule); vagotomized + ethanol-treated (diagonal plus horizontal); chronic celiac ganglionectomized (vertical rule); and ganglionectomized + ethanol-treated rats (diagonal rule). Ordinate: output or HCO_3^- (µeq/30 min). The values shown are means ± SEM of at least 10 exeriments.
$^*p < 0.02$; $^{**}p < 0.01$; $^{***}p < 0.001$.

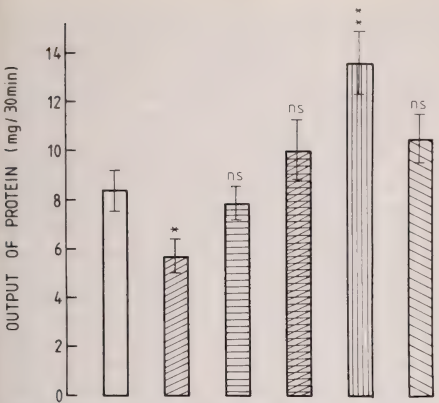


Fig. 9. Protein output of bile-pancreatic juice of control (blank square); chronic ethanol-fed (diagonal rule); chronic vagotomized (horizontal rule); vagotomized + ethanol treated (diagonal plus horizontal); chronic celiac ganglionectomized (vertical rule); ganglionectomized + ethanol-treated rats (diagonal rule). Ordinate: output of protein (mg/30 min). Values shown are means ± SEM of at least ten experiments. $^{*}p < 0.02$; $^{**}p < 0.01$.

of protein synthesis (synthesizing enzymes concerning neurotransmission) is able to increase or to decrease in a normal pattern, depending on the amount and time of alcohol intoxication (5).

Moreover, the rise of the neurotransmitter synthetic rate in ethanol-fed rats is observed long before alcohol-induced decline in body weight (5). Ethanol feeding slightly reduced the weight of the submaxillary gland and did not modify that of the pancreas. Some remarkable changes, however, occurred when alcohol treatment was superimposed on denervated glands. It is well known that in rats, submaxillary gland chronic parasympathetic decentralization markedly reduces the gland's weight (12); on the other hand, the same procedure has recently been reported to increase the pancreas weight by nearly 100% (3, 4, 13). In the salivary gland, ethanol did not modify the atrophy induced by parasympathetic decentralization, either when the chordatympany section was performed at the start of alcohol feeding, or when decentralization was carried out three weeks before the alcohol treatment stage was completed. Moreover, ethanol did not modify the trophic effects produced by the combined sympathetic and parasympathetic decentralizations.

These findings, in agreement with our previous hypothesis, indicate that the trophic effects of alcohol feeding on the salivary gland are mediated through influences from the central nervous system.

In the pancreas, the findings are more complex and are probably related to the more intricate innervation. In a normal innervated pancreas, ethanol does not induce weight changes (29). On the other hand, it completely blocks, especially on the body-tail segment, the striking pancreatic hypertrophy triggered by truncal vagotomy. The mechanism of this ethanol-elicited trophic suppression, which reaches levels even lower than control values, is probably related to inhibitory impulses starting at the central nervous system and reaching the pancreas via the splanchnic nerves and the celiac ganglia (29). This interpretation is supported by the fact that when chronic ethanol intoxication is superimposed on a pancreatic gland subjected to truncal vagotomy plus celiac ganglionectomy, no trophic changes are observed.

The same line of thought is supported by the present results on ChAc activity. It is well known that in the submaxillary gland, the only sources of cholinergic innervation are the parasympathetic fibers that come through the chordalingual nerve (30). Therefore, the finding that gland decentralization, either at the beginning of alcohol treatment or three weeks before completion of the alcohol-fed stage, prevents the increase of ethanol-induced ChAc activity strongly suggests that the peripheral effects of chronic alcoholism are the result of increased traffic impulses from the parasympathetic central nervous system. Along these lines, it has been reported that chronic sympathetic decentralization or denervation induces increased ChAc activity (18, 31). This parasympathetic-augmented tone, triggered by removal of sympathetic influences, resembles that obtained after chronic ethanol intoxication. Since in these two circumstances parasympathetic decentralization can abolish the rise in cholinergic tone, it is tempting to conclude that both procedures elicit this phenomenon through similar mechanisms.

TABLE 3

Choline Acetylase and Acetylcholinesterase Activities in Medulla of Alcohol-Fed Rats

(n = 8)

	Choline acetylase (μmol Ach/gm/hr)	Acetylcholinesterase (μmol/gm/hr)
Control	6.14 ± 0.27	457.4 ± 21.65
Ethanol	9.17 ± 0.22*	395.0 ± 30.49†

Values are means ± SEM of n experiments.

$^{*}p < 0.02$ $^{\dagger}p < 0.05$ when compared with control groups.

It has been reported (31) that the increase in ChAc activity of the salivary glands is the result of enhanced traffic of secretory impulses in the parasympathetic nerves and of collateral sprouts from them.

The ChAc changes in the pancreatic gland are much more complex, undoubtedly because cholinergic fibers arrive at the gland through more intricate pathways. Indeed, anatomic and biochemical studies (3, 4, 6, 25) have demonstrated that cholinergic innervation of the pancreas depends on impulses not only from parasympathetic centers, but also from peripheral "intermediate" autonomic centers ("antral," "duodenal," and "celiac") which influence pancreatic activity (29). Besides, when these centers are deprived of central modulation (as in vagotomy), they become hyperactive and may act as primary neurones (32). This is evidenced by alcohol administration (33).

Further insight results from the analysis of the effects of alcohol feeding on normally innervated pancreas and glands subjected to vagotomy or celiac ganglionectomy, or to both procedures combined. Chronic vagotomy induces a marked reduction of ChAc activity. A reduction in enzyme activity of this magnitude is obtained in other autonomically decentralized organs (10, 12, 13). On the other hand, alcohol feeding evokes a marked increase of ChAc activity (nearly 30%) in the whole gland. When vagotomized animals are also subjected to ethanol intoxication, ChAc activity changes are different in each segment of the gland. At the head, enzyme values are partially reversed, reaching control levels; in the body-tail segment, results do not differ from those observed in rats fed alcohol alone.

Comparing changes in the submaxillary gland and the pancreas, it is evident that ethanol exerts its effects on the pancreas through nervous pathways other than the vagal trunk, and that after the vagus is cut, alcohol activates what we have called "the intermediate autonomic centers," mainly the "antral" and "duodenal" brains. These conclusions are based on the following:

- Chronic celiac ganglionectomy reduces ChAc activity in the head of the gland only, in a magnitude like that observed after truncal vagotomy. This suggests that the cholinergic vagus fibers that reach the pancreas head pass mainly through the celiac branch of the vagus nerve.
- The vagus is practically the only source of cholinergic fibers that innervates the pancreas from the central nervous system centers. This is confirmed by a recent finding showing that bilateral splanchnicectomy does not modify ChAc activity in the whole pancreatic gland (unpublished observation, 1983). This is unexpected, since in other animals (29) there are several indications that cholinergic fibers pass through the splanchnic nerves.
- The cholinergic innervation of the body-tail segment is dependent mainly on impulses coming from the "antral" and "duodenal" autonomic brains (29). This is suggested by several recent experimental findings. Chronic section and reanastomosis of the duodenum at the Vaterian level neither modifies ChAc activity in the head nor induces an increase in enzyme activity at the gland's body-tail segment. Besides, a remarkable increase weight of the head is found. Our interpretation is that this surgical procedure interrupts pancreatic inhibitory impulses coming from the lower segments of the gut. These would normally exert a restraining influence on both the "duodenal" and "antral" autonomic brains. After duodenotomy, they "liberate" and become hyperactive, reflected mainly in the body-tail segment.
- After truncal vagotomy, alcohol feeding reverses ChAc values to control levels in the head, but to chronic alcoholism alone in the body-tail segment. According to our interpretation, this would be an indication that the body-tail segment is subjected to the control of the "antral" and "duodenal" autonomic brains, the cholinergic primary neurones of which would develop hypersensitivity to alcohol after losing the modulation (vagotomy) of the central cholinergic centers.

Despite the possible role of peripheral autonomic centers, the main effect of chronic ethanolism on cholinergic tone is triggered by the central nervous system. The augmented ChAc activity observed in the medulla of chronic alcohol-fed rats confirms this hypothesis and is in agreement with results reported in the literature (34, 35). Besides, the activity of acetylcholinesterase, responsible for inactivation of the cholinergic neurotransmitter, was slightly but significantly reduced, as in other reports on the central nervous system (36) and on some peripheral effectors, such as dog pancreas (25). On the other hand, chronic ethanol feeding did not induce significant changes in enzyme activity of the submaxillary gland, but did slightly increase such activity in the adrenal gland of the rat (2). However, in spite of different effects on these structures, modification of acetylcholinesterase activity seems not to play a major role in the development of the increased cholinergic tone induced by chronic alcoholism.

Secretions evoked by exogenous autonomic sialagogs in the submaxillary glands are mediated via muscarinic cholinergic receptors and sympathetic stimulation via α and β adrenoceptors (37, 38). As in our previous findings, chronic ethanol treatment induced a remarkable decrease in the sensitivity of the submaxillary glands to exogenous methacholine, evidenced by a shift to the right of the dose-response curve when compared with controls (1). Responsiveness of an effector organ to chemical or nerve stimuli increases when the organ has been previously decentralized (10, 12). In addition, in the submaxillary gland, when parasympathetic neurones are disconnected from the central nervous system (section of the chordalingual nerve), ChAc activity is significantly decreased and postjunctional supersensitivity develops (16, 39). This surgical procedure reverses the subsensitivity induced by chronic ethanol treatment, as indicated by the fact that decentralization produced similar displacements to the left of the dose-response curves to methacholine in both alcoholic and control animals.

Two hypotheses have been suggested concerning the effect of alcohol intoxication and its mechanism at the neuroeffector level.

- One hypothesis postulates that chronic alcohol ingestion depresses response by direct action on the cells of the effector organ, diminishing the organ's capacity of response and therefore perhaps eliciting reflexively an increase in nervous activity.
- The second hypothesis is that ethanol acts indirectly, via the central nervous system (autonomic centers), thereby increasing the traffic of impulses through the nerve endings that reach the target organ.

The trophic and functional changes observed in the submaxillary gland are strong arguments for the second postulate. Indeed, it is remarkable how submaxillary cells subjected to chronic alcohol intoxication (subsensitivity) show, after nerve section, a high degree of supersensitivity, implying an almost intact postsynaptic normal secretory machinery.

Because of the more intricate neurohormonal regulation of bile-pancreatic secretion, the interaction of ethanol either alone or combined with the different surgical procedures on the peripheral innervation of the pancreas makes clearcut interpretation of the functional findings more difficult. Yet, analysis of the hydrelatic response indicates that chronic alcoholism induces a significant increase in bicarbonate output. Chronic vagotomy alone does not modify this parameter (13), but when both experimental procedures are combined, there is no doubt that vagotomy prevents the changes evoked by chronic alcohol feeding alone. On the contrary, chronic celiac ganglionectomy depressed bicarbonate output but did not prevent the excitatory effects on bicarbonate secretion elicited by chronic alcoholism. After celiac ganglionectomy the vagus pathway remains partially intact (the gastric branch), allowing ethanol to exert its excitatory influences (6–8).

Concerning the bile-pancreatic ecbolic secretory responses, it is also evident that chronic vagotomy was able to abolish the inhibitory effects on protein output evoked by alcohol feeding. Similarly, chronic celiac ganglionectomy, which itself triggers a significant excitatory protein secretion, prevented the depression observed in animals subjected to alcoholism alone.

The resemblance between the functional results obtained for the submaxillary glands and the pancreas is striking, since the effects of alcohol on the several parameters of the two structures may be modified by interfering with the autonomic innervation of the organs. Although direct action of alcohol on the cells of autonomic effector organs cannot be ruled out, it is evident that the main effect of chronic alcoholism is on the autonomic central nervous system, resulting in increased traffic of impulses through several branches. This high cholinergic tone, at least in the submaxillary and pancreatic glands, is certainly responsible for the trophic, biochemical, and functional alterations observed.

The intimate mechanism by which these changes are induced cannot yet be clearly explained. One wonders whether, in both glands studied, the surgical procedures modify the effects of alcohol treatment, or whether alcohol alters the trophic, biochemical, and functional changes induced by interruption of cholinergic pathways. This line of thought needs further investigation, but undoubtedly the changes induced by alcoholism may explain some clinical observations related to the pathophysiologic mechanisms of alcoholic pancreatitis, as well as disturbances in trophic and functional parameters in salivary glands.

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^{3}H-QNB Binding in Submaxillary Glands Subsensitized by Chronic Alcohol Feeding

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Abstract

Chronic ethanol feeding was induced in female rats by giving them alcohol as the only source of liquid for either 6 or 12 weeks. In both groups, dose-response curves to methacholine shifted to the right, by nearly 0.3 and 0.5 log units, respectively. In spite of the subsensitivity obtained after chronic ethanol treatment, the number of ^{3}H-QNB binding sites remained unchanged. Chronic parasympathetic decentralization induced supersensitivity to the sialagog agonist methacholine in both untreated and chronically ethanol-treated rats. The shift to the left of the dose-response curves of the subsensitive glands in ethanol-treated rats was similar to that observed in untreated rats. Also, parasympathetic decentralization induced an increase in the ^{3}H-QNB binding sites in both untreated rats and rats fed ethanol for 6 or 12 weeks. These results show that alcohol-induced subsensitivity is not related to a change in the total number of muscarinic receptors. The subsensitive glands became supersensitive when parasympathetic decentralization was performed. Since section of the chordalingual nerve induced an increase in the total number of muscarinic receptors in glands from chronic ethanol-treated rats, we concluded that the modulatory mechanisms which regulate the sensitivity of the effector cells remained functional.

It has been reported that long-term ethanol feeding induces marked hyperactivity of both branches of the autonomic nervous system. Thus, in the submaxillary gland of the rat, both choline acetylase activity and endogenous noradrenaline concentration increase after 12 weeks of ethanol treatment (1). In addition, secretory responses to exogenous adrenergic or cholinergic secretagogs decrease in ethanol-fed rats. This subsensitivity has been related to the chronic autonomic hyperactivity induced by ethanol (1).

Subsensitivity has been reported to develop after nerve or drug overstimulation of the effector organ. Decrease in responses induced by several procedures has been associated with decrease in number of receptor sites (2, 3). The present experiments were designed to study whether ethanol-induced subsensitivity to cholinomimetic agents is related to changes in number of receptors. For this purpose, binding of the muscarinic radioligand ^{3}H-QNB was determined in innervated and parasympathetic-decentralized submaxillary glands after 6 and 12 weeks of ethanol treatment. In addition, the secretory responses induced by exogenous methacholine were determined in an attempt to correlate the biochemical and functional changes induced by long-term ethanol treatment.

Methods

Female Wistar rats weighing 180–230 gm (3 months old) were divided into two experimental groups. One group was allowed to drink only a

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solution of ethyl alcohol according to the following schedule: first week, a 5% solution (v/v); the next 2 weeks, 10% (v/v); the following week 15% (v/v); the fifth week the dose was increased to 25% (v/v), until on the 90th day, the animals received a solution of 32% (v/v). The second experimental group was allowed to drink water ad libitum. Parasympathetic decentralization of the right submaxillary gland of each animal was done 24 hours before the ethanol treatment was started. Decentralization was achieved by section of the chordalingual nerve under ether anesthesia.

The left submaxillary gland was considered the control. Half of the animals belonging to either group were killed at the end of the 6th week of ethanol treatment, and the other half were killed after 12 weeks. Animals were anesthetized with Embutal (66 mg/kg); both submaxillary glands were carefully dissected, dried, and weighed. Glands were immediately frozen and stored for binding studies.

For estimation of the secretory responses, as previously described, rats were anesthetized with chloralose (100 mg/kg) intravenously after ether induction. After the trachea was intubated, both submaxillary ducts were exposed and cannulated with fine glass cannulae, which delivered 91 drops from 1 ml of distilled water. Dose-response curves for methacholine were obtained by the sequential injection via the femoral vein of 0.1, 1, 3, and 10 μg/kg of the drug.

Binding Studies. Submaxillary glands were cut into small pieces and homogenized in 10 vol of Tris-HCl, pH 7.5, with an Ultra-Turrax, setting 7, and centrifuged 10 min at 1000 g. The pellet was then resuspended and centrifuged again. Both supernatants were mixed and centrifuged at 35,000 g for 45 min. The pellet was washed, resuspended, and centrifuged again for 45 min at 35,000 g. The final pellet was resuspended in buffer Tris, pH 7.5, to obtain a final concentration of 1 mg of membrane protein/ml. All procedures during membrane preparation were carried out at 0°–4°C.

In order to perform the binding assay, 100 μl of the membrane suspension was incubated with various concentrations of ^{3}H-QNB ranging from 0.01 nmole to 2.5 nmole in a final volume of 5 ml. Nonspecific binding was determined at each concentration by incubation with 0.3 μM atropine. Equilibrium was reached in 90 min at 37°C (4). Incubation was stopped by the addition of 3 ml of the same incubation buffer, and membranes were collected on Whatman GF/B paper and washed three times with 5 ml of buffer.

Radioactivity in the filter was assayed in 5 ml of toluene scintillation fluid containing 0.6 g 1,4-bis 2 (5-phenyl-oxazolyl) (POPOP); 4 g 2,5-diphenyloxazole (PPO), and 5 ml ethanol per liter of toluene. The samples were counted in a Packard liquid scintillation spectrometer with an efficiency of 35%. It has been demonstrated that in the ^{3}H-QNB binding assay, there is a relationship between the apparent affinity (K_D) and the concentration of the receptors in the incubation mixture (4). Therefore, protein concentration in the assay was monitored to remain as constant as possible (20μg/ml). Protein concentration was determined following the method described by Lowry (5), using bovine serum albumin as standard.

Both the density of receptors (Bmax) and their affinity (K_D) were determined from saturation experiments with at least 7 concentrations of the radioligand. The data were plotted as bound/free versus bound (6) and calculated by an unweighed linear regression analysis. Statistical analysis was performed using Student's *t* test.

Drugs. The following drugs were used: 1-benzilic-4,4′-^{3}H-quinuclidynyl benzilate (33,1 Ci/mmol, New England Nuclear); methacholine chloride and atropine sulphate (Sigma Chemical Company, St. Louis, Mo).

Results

In this series of experiments, the body weight of rats treated with alcohol was found to be 10% lower than the weight of controls; this difference did not reach statistically significant levels. The wet weight reduction of the right submaxillary gland by chronic parasympathetic decentralization was about 33% (controls: 192.7 ± 11.3 to 130 ± 14.4, $p < 0.025$). Chronic ethanol treatment by itself reduced glandular weight by nearly 20% but did not further reduce the wet weight of the glands that had undergone long-term decentralization.

Ethanol feeding for either 6 or 12 weeks produced subsensitivity to methacholine. In both experimental groups, the magnitude of the subsensitivity obtained was similar. Thus, the dose-response curves to methacholine were shifted to the right of the control curves by nearly half log unit (Figs. 1, 2).

Ethanol feeding did not change the affinity of ^{3}H-QNB for muscarinic receptors in the submaxillary gland membranes, neither after 6 nor after 12 weeks of ethanol treatment (Table). Similarly, no significant differences were obtained in the

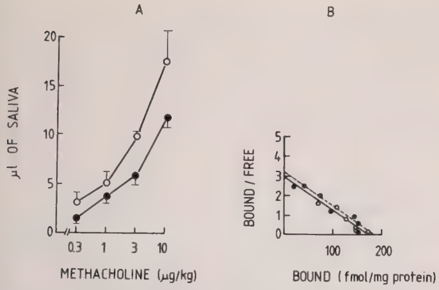

Fig. 1. Effects of 6 weeks of ethanol administration on secretory responses to methacholine and ^{3}H-QNB binding. **A** Dose-response curves to methacholine from control submaxillary glands (○) and alcohol-fed rats (●). Ordinate: microliters (µl) of saliva. Abscissa: methacholine in µg/kg. Shown are means ± SEM of at least 4 experiments. **B** Rosenthal (6) plot of binding of ^{3}H-QNB of membranes from controls (○) and alcohol-fed rats (●). Nonspecific binding was determined in presence of 1 µM atropine. Typical experiment shown was repeated at least 3 times.

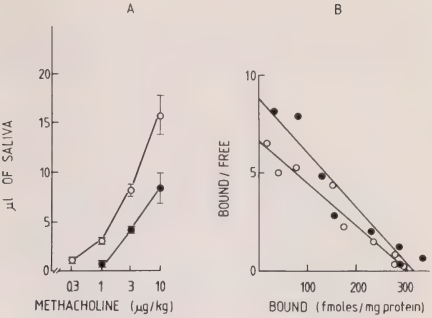

Fig. 2. Effects of 12 weeks of ethanol administration on secretory responses to methacholine (**A**) and ^{3}H-QNB binding (**B**). (For details see caption of Fig. 1.)

density of receptors (Bmax) between gland membranes from ethanol-treated rats and controls (Figs. 1, 2, and Table).

Since no changes were found in the number of muscarinic receptors in innervated glands from ethanol-treated rats in spite of the subsensitivity obtained to methacholine, we investigated whether other procedures known to induce changes in sensitivity to parasympathomimetic agents would modify the subsensitivity observed in ethanol-treated rats. Using the same parameters, we found that parasympathectomy induced supersensitivity to methacholine in glands of controls and of rats fed ethanol for 12 weeks (Fig. 3). The supersensitivity was evidenced by an increase in the potency of methacholine for the secretory responses. Parasympathetic decentralization induced in both control and alcohol-fed animals a significant increase in the density of receptors (Bmax) for ^{3}H-QNB binding (Fig. 4). The increase was of similar magnitude in both: 50% in controls and 47% after ethanol treatment (Table). On the other hand, affinity (K_D) was significantly decreased ($p < 0.05$) by parasympathectomy only in control glands; no such changes were seen in membranes from ethanol-treated rats (Table). After 12 weeks of ethanol treatment, decentralization produced similar changes in the density of receptors in the glands of both controls and ethanol-fed rats (Fig. 5, Table). The differences in affinity observed in the group treated for 6 weeks could not be detected after 12 weeks of parasympathetic decentralization (Table).

Discussion

In agreement with previous results, ethanol treatment during either 6 or 12 weeks induced a remarkable decrease in the submaxillary secre-

TABLE

^{3}H-QNB Binding in Membranes of Innervated and Chronic Parasympathetic-decentralized Submaxillary Glands of Controls and Alcohol-fed Rats

	6-Week Treatment		12-Week Treatment	
Treatment	K_D (pM)	Bmax (fmol/mg)	K_D (pM)	Bmax (fmol/mg)
None	61.8 ± 5.7	168 ± 3.5	61.3 ± 5.9	301 ± 10.4
Parasympathectomy	40.6 ± 3.5*	253 ± 21.5†	58.6 ± 11.4	402 ± 13.1‡
Ethanol	51.6 ± 7.4	172 ± 5.1	62.7 ± 17	328 ± 13.1
Parasympathectomy + ethanol	52 ± 9	254 ± 18^c	50.5 ± 3.4	459 ± 13.7§

Affinity (K_D) and maximal ^{3}H-QNB binding (Bmax) values were obtained from linear regression analysis of Rosenthal(6) plot. Values are mean ± SEM of at least 3 experiments per group; ‡$p < 0.001$; §$p < 0.005$; †$p < 0.025$; *$p < 0.05$, compared to respective contralateral innervated gland.

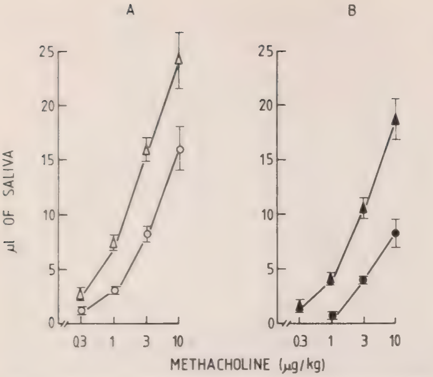

Fig. 3. Effects of chronic parasympathetic decentralization on sensitivity to metacholine in ethanol-fed rats (12 weeks) and controls. **A** Dose response curves to methacholine from control submaxillary glands (○) and chronic parasympathetic decentralized glands (△). **B** Dose response curves to methacholine from control glands treated with alcohol (●) and chronic parasympathetic decentralized glands treated with alcohol (▲). Ordinates: saliva secreted (µl). Abscissae: doses of metacholine in µg/kg. Means ± SEM of at least 4 experiments are shown.

tory responses to exogenous administration of methacholine (1).

Subsensitivity obtained after either nerve hyperstimulation or prolonged exposure to agonists has been reported to be associated with a decrease in the number of receptors in different effector organs (2–3). The present results show, however, that alcohol-induced subsensitivity is not related to a diminished number of ^{3}H-QNB binding sites.

Note that a diminished number of receptors in subsensitive tissues has been described mainly for adrenoceptors but down-regulation of muscarinic receptors is not a general response to overstimulation. Thus, in the same salivary gland, chronic physostigmine treatment does not modify the ^{3}H-QNB binding sites (7); on the other hand, in several brain regions, overstimulation by oxotremorine induces a significant reduction in the number of ^{3}H-QNB binding sites (8).

Furthermore, the finding of an unchanged number of receptors does not absolutely exclude receptor participation in ethanol-induced subsensitivity. In this respect, antagonist binding, which has been extensively employed elsewhere, as well as in the present experiments, does not necessarily reflect the behavior of a putative small population of physiologically relevant receptors. Thus, it has been shown (9) that the maximal binding for the agonist oxotremorine was only 25% of that measured for the antagonist ^{3}H-QNB.

Long-term ethanol feeding may exert a direct effect on the cell membrane by modifying its lipid composition, which results in increased rigidity (10–11); therefore it may affect the ability to modulate the number of receptors in response to chronic ethanol feeding. However, this seems not to be the case, since parasympathetic decentralization of the submaxillary gland induced an increase in the number of receptors in both controls and ethanol-treated rats. Thus, it can be concluded that after chronic ethanol treatment, glands are able to modulate their receptor number in response to changes in neuronal input as efficiently as glands from nonalcoholic rats. Moreover, the subsensitive gland from ethanol-fed rats was not only able to modulate the number of receptors after parasympathetic decentraliza-

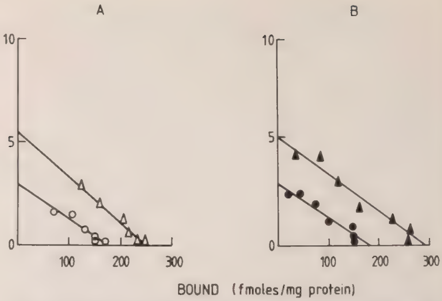

Fig. 4. Effects of chronic parasympathetic decentralization on ^{3}H-QNB binding on membranes from controls and ethanol-treated rats (6 weeks). **A** Rosenthal (6) plot of binding of ^{3}H-QNB from control submaxillary glands (○) and chronically parasympathetic-decentralized glands (△). **B** Rosenthal (6) plot of binding of ^{3}H-QNB from control gland treated with alcohol (●) and decentralized gland treated with alcohol (▲). Nonspecific binding was determined in the presence of 1 µM atropine. Typical experiment shown was repeated at least 3 times.

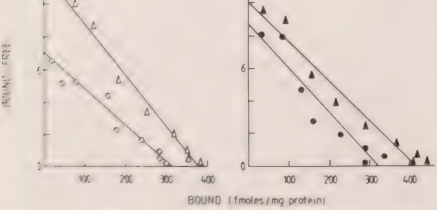

Fig. 5. Effects of chronic parasympathetic decentralization on ^{3}H-QNB binding in membranes from controls (A) and rats treated with ethanol for 12 weeks (B). For details see legend to Fig. 4.

tion but also to modulate the gland's physiological response. This was evidenced by the finding that parasympathectomy induced postjunctional supersensitivity to methacholine in both ethanol-treated and untreated rats. Thus, a subsensitive organ is able to become supersensitive in the same magnitude as can a normally sensitive control organ.

The present results also show that the response to the cholinergic agonist in ethanol-treated rats never reached the level obtained in untreated rats in spite of the fact that both showed similar displacements of the dose-response curves. This finding may indicate that although in ethanol-treated glands, modulatory mechanisms remain functional, this modulation is expressed at a lower level of response than in control glands.

The finding that parasympathetic-decentralized glands not exposed to full cholinergic input also developed a certain degree of subsensitivity after ethanol treatment suggests that the increase in cholinergic tone is not the only cause of the subsensitivity observed and therefore that some other mechanisms are involved. After partial removal of the intraglandular parasympathetic ganglia, a higher degree of supersensitivity is obtained than in submaxillary glands that have only been decentralized. (12). Thus, it seems that a certain degree of cholinergic activity remains in the latter glands. Also, modulation of sensitivity in salivary glands is more related to organ activity than to neuronal input (13, 14). Thus, under our experimental conditions, even if muscarinic-mediated responses are decreased, hyperactivity of the organ may be induced by sympathetic overstimulation of the gland, since both the muscarinic and the α-adrenoceptors' secretory responses are known to share the same secretory mechanism (15).

Finally, one cannot dismiss a certain direct action of alcohol on the secretory cells. A direct effect of ethanol on the effector cells has been described in other organs. In addition to changes in membrane lipid composition mentioned above, alcohol affected several metabolic functions of the heart muscle cells, causing mitochondrial damage, deficiencies in the contractile machinery, and diminished protein synthesis (10–11, 17). Thus, although the basic mechanism by which alcoholism induces changes in the sensitivity of the gland remains unclear, the present results clearly show that subsensitivity to methacholine is not associated with a decrease in the total number of receptor sites as evidenced by the ^{3}H-QNB binding.

Acknowledgments

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The Effect of DL-Ethionine, Cholecystokinin, and Cerulein on Pancreatic Secretion and Tissue Composition in Rats

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Abstract

We investigated whether peptides stimulating pancreatic growth (cholecystokinin and cerulein) could reverse the damage to pancreatic secretion and tissue induced by DL-ethionine in rats. CFY male rats were treated twice a day intraperitoneally with 20 U/kg of cholecystokinin (CCK) and with 1 μg/kg of cerulein; we also administered DL-ethionine 150 mg/kg once a day and ethionine in combination with CCK or cerulein for 15 days. Rats treated with saline solution served as controls. On the 16th day, pancreatic juice was collected following injection of 8 U kg of secretin-plus-CCK. Pancreatic tissue was subjected to biochemical analysis, histologic investigation, and electron microscopy.

Ethionine decreased pancreatic secretion and lipase output. Both peptides failed to counteract the effect of ethionine on the output of lipase in stimulated pancreatic secretion. Ethionine induced atrophy of the gland and decreased total pancreatic DNA and RNA content and amylase and lipase activity.

Both peptides stimulated pancreatic growth, total pancreatic DNA content, and trypsin and amylase activity. CCK given in combination with ethionine reversed the negative effect of ethionine on pancreatic tissue composition, but could not reverse the decrease in DNA content. Cerulein, on the other hand, could not reverse the ethionine-induced decrease in pancreatic weight or the decrease in total pancreatic RNA content and lipase activity. We conclude that neither CCK nor cerulein can completely repair damage to the pancreas induced by ethionine. CCK seems more potent in this respect than cerulein.

One of the main problems in chronic pancreatitis, when pancreatic function is already impaired by damage to the pancreatic acinar parenchyma, is how the damaged gland can be repaired and pancreatic enzyme secretion normalized as much as possible.

To investigate this problem, we induced damage to the pancreatic acinar parenchyma in rats by giving them DL-ethionine for 15 days. We studied its effect on pancreatic secretion and tissue composition when administered alone and in combination with cholecystokinin (CCK) and cerulein.

It is well known that ethionine impairs pancreatic enzyme secretion (1) and induces degenerative changes in the pancreatic glandular parenchyma (1–6). CCK (7–12) as well as cerulein (13–15), which is an analog of the C-terminal decapeptide of CCK, exert trophic action on the pancreas in rats.

Materials and Methods

Pilot Experiments. Twenty-eight CFY male rats, weighing 250 gm, were anesthetized by urethane and effective single doses of the peptides (administered intraperitoneally) were determined. CCK (Kabi, Stockholm) in a 20 U/kg dose

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(9 rats) or cerulein (Farmitalia, Milan) in a 1 μg/kg dose (10 rats) increased pancreatic protein output significantly (Fig. 1). DL-ethionine (Vega, Tucson) when given intraperitoneally for three days in a dose of 150 mg/kg significantly reduced the effect of 20 U/kg of CCK (9 rats).

Treatments. We treated 60 CFY male rats in two experimental series for 15 days. Each series contained four groups.

In the first series (I), Group 1 (7 rats; 256 ± 13 gm; mean ± SEM) was treated with saline solution twice a day; Group 2 (7 rats; 261 ± 7 gm) was treated with 20 U/kg of CCK twice a day; Group 3 (7 rats; 259 ± 10 gm) was treated with 150 mg/kg of DL-ethionine once a day; Group 4 (7 rats; 259 ± 7 gm) was treated with 20 U/kg of CCK twice a day, combined with 150 mg/kg of DL-ethionine once a day.

In the second series (II), Group 1 (8 rats; 160 ± 2 gm) was treated with saline twice a day; Group 2 (8 rats; 160 ± 2 gm) was treated with 1 μg/kg of cerulein twice a day; Group 3 (8 rats; 158 ± 4 gm) was treated with 150 mg/kg of DL-ethionine once a day; Group 4 (8 rats; 158 ± 3 gm) was treated with 1 μg/kg of cerulein twice a day, combined with 150 mg/kg of DL-ethionine once a day.

In both experimental series, the rats were anesthetized by urethane on the sixteenth day. Body weight was measured. A polyethylene cannula was introduced into the duodenal end of the common bile duct and the duct was ligated at the hepatic hilum. Pancreatic secretion was stimulated by 8 U/kg of secretin (GIH Lab, Stockholm); CCK was given as a bolus into the femoral vein; and pure pancreatic juice was collected for 60 min. The volume of the juice was measured.

Biochemical Analysis. The rats were exsanguinated from the abdominal aorta; each pancreas was removed and weighed; 150 mg of the gland was homogenized in 5 ml of 0.25 M sucrose solution with a Potter-Elvenhjem Teflon glass homogenizer. After centrifugation (at 1500 g for 10 min) the supernatant was analyzed for protein level (16), for trypsin activity after trypsinogen activation by enterokinase (17), and for activity of amylase (18) and lipase (19). Pancreatic tissue (250 mg) was homogenized in distilled water (5 ml), then DNA and RNA were extracted (20). DNA was determined by using diphenylamine (21), RNA by orcinol-HCl (22) using D-ribose as standard. These methods were used for estimating protein and enzyme secretion in the pancreatic juice. Statistical analysis was performed using Dunnett contrasts (23). The results were expressed as mean ± SEM.

Histology and Electron Microscopy. Specimens of the pancreas of rats in each group were fixed in a 6% buffered formalin solution. The specimens were embedded in paraffin; sections

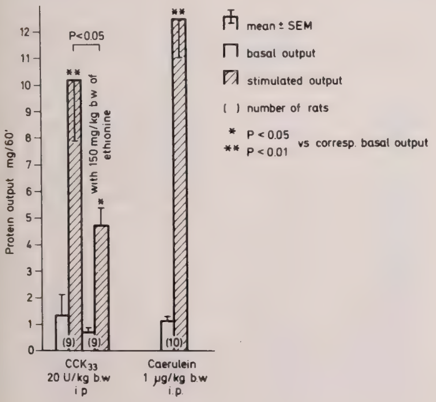


Fig. 1. Top left Effect of single doses of intraperitoneal (i.p.) CCK, cerulein, and ethionine for 3 days on pancreatic protein secretion.

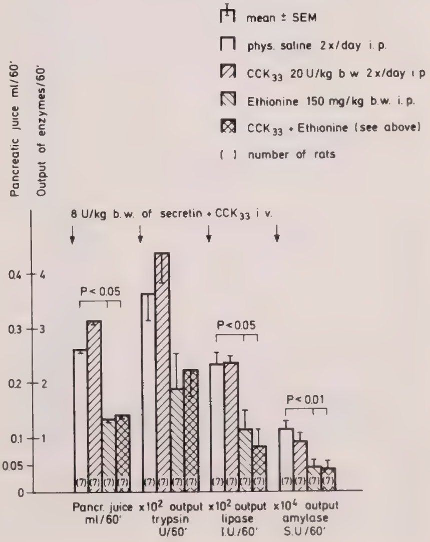


Fig. 2. Right Effect of intraperitoneal treatment with CCK, ethionine, and CCK-plus-ethionine (each for 15 days) on stimulated pancreatic secretion.

were cut, 5 μm thick; these were stained with hematoxylin-eosin and submitted to light microscopy.

For electron microscopy, small samples of the pancreas were treated with Karnovsky's fixative (24) for two hours, and after washing overnight in sodium cacodylate buffer, postfixed in 1% osmium tetroxide for 90 minutes at 4°C; 0.13 mol/l sodium cacodylate buffer was used to adjust all fixatives to pH 7.4. After dehydration in a graded series of ethanol solutions and transferrence to propylene oxide, the pieces were embedded in Durcupan ACM or Spurr's epoxy resin. Ultrathin sections, cut on a Reichert Om U2 ultramicrotome, were stained first with 20% uranyl acetate, dissolved in methanol, then with lead citrate, as described by Reynolds (25), and studied in a JEOL TEMSCAN-1000 electron microscope.

Results

When measured on the 16th day, the body weight of the ethionine-treated rats was found to be significantly less than the body weight of control rats (260 ± 18 gm vs 312 ± 13 gm; 212 ± 6 gm vs 261 ± 5 gm) ($p < 0.01$). Neither CCK nor cerulein affected the ethionine-induced decrease in body weight.

Pancreatic Secretion. CCK treatment had no effect on pancreatic secretion. Ethionine, however, decreased the volume of pancreatic juice and the output of lipase and amylase. CCK combined with ethionine did not counteract the effect of ethionine on pancreatic secretion (Fig. 2).

Cerulein treatment increased the volume of juice and the output of trypsin and amylase in it. Ethionine decreased the volume of pancreatic juice and the output of lipase and amylase. Cerulein in combination with ethionine corrected the effect of ethionine on the volume of juice and output of amylase, but did not restore lipase output (Fig. 3).

Pancreatic Tissue. In the first experimental series, CCK increased pancreatic weight (the relation of pancreatic weight to body weight in the CCK-treated group was 4.40% ± 0.21%; control group, 3.05% ± 0.14%; $p < 0.05$). CCK increased total pancreatic trypsin, amylase, and DNA (Fig. 4). Ethionine decreased pancreatic weight (relation of pancreatic weight to body weight in the ethionine-treated group was 1.89% ± 0.24%; in the control group, 3.05% ± 0.14%; $p < 0.01$). Ethionine decreased total pancreatic lipase and DNA and RNA.

CCK administered in combination with ethionine counteracted the effect of ethionine on pancreatic weight, total pancreatic lipase and RNA content, without influencing the reduction of total pancreatic RNA of ethionine. Although ethionine given alone did not affect total pancreatic trypsin activity, when given in combination with CCK it counteracted the stimulative effect of CCK (Fig. 4).

Histologic analysis of specimens treated with CCK revealed acinar cells with the cytoplasm full of zymogens (Fig. 5), as compared with control pancreas (Fig. 6). Ethionine induced degeneration of acinar parenchyma, with pyknosis of cell

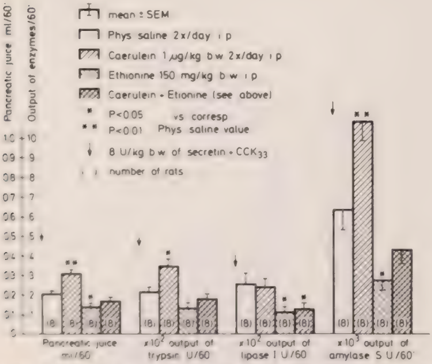


Fig. 3. Left Effect of intraperitoneal treatment with cerulein, ethionine, and cerulein-plus-ethionine (each for 15 days) on stimulated pancreatic secretion.

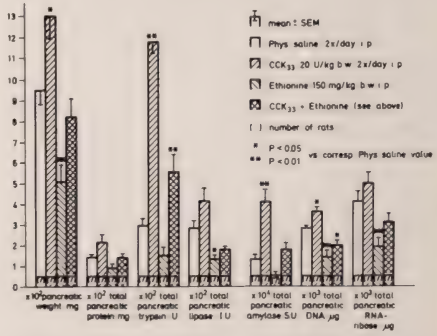
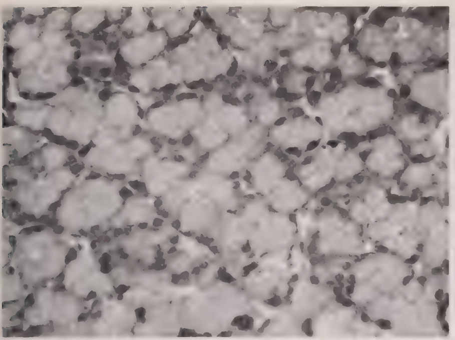
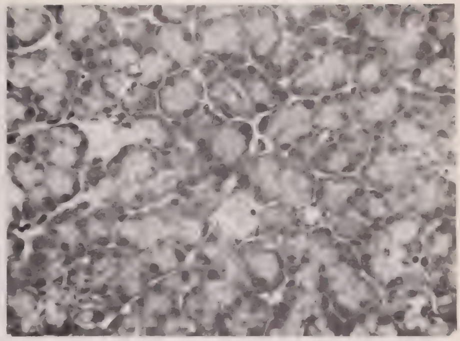


Fig. 4. Right Effect of intraperitoneal treatment with CCK, ethionine, and CCK-plus-ethionine (each for 15 days) on pancreatic tissue composition.





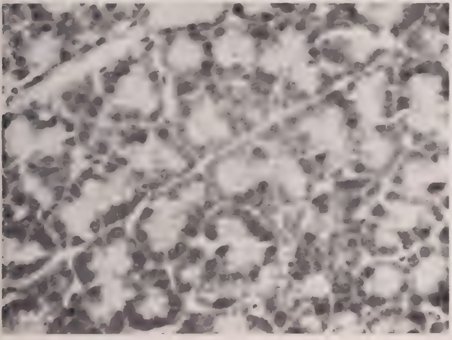


Fig. 5. Top left Histological picture of CCK-treated rat pancreas: acinar cells full of zymogen granules (HE × 120, slightly reduced).

Fig. 6. Top right Histological picture of saline-treated (control) rat pancreas (HE × 120, slightly reduced).

Fig. 7. Left Histological picture of ethionine-treated rat pancreas: inhomogeneous staining of acinar cells with pyknosis of their nuclei (HE × 140, slightly reduced).

nuclei (Fig. 7). The fine structure of the CCK-treated parenchyma showed an increased number of enlarged blood capillaries (Fig. 8), as compared with control pancreas (Fig. 9). Ethionine induced distention of cisternae of granular endoplasmatic reticulum with pyknotic nuclei (Fig. 10).

In the second experimental series, cerulein increased pancreatic weight. The ratio of pancreatic weight to body weight in the cerulein-treated group was 5.15% ± 0.10%; in the control group, it was 3.74% ± 0.20% ($p < 0.01$). Cerulein increased total pancreatic trypsin and amylase activity and total pancreatic DNA and RNA (Fig. 11).

Ethionine decreased pancreatic weight. The ratio of pancreatic weight to body weight in the ethionine-treated group was 2.57% ± 0.28%; in the control group the ratio was 3.74% ± 0.20%; $p < 0.01$.

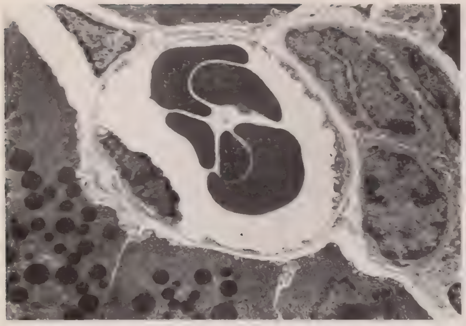
Cerulein in combination with ethionine counteracted ethionine's effect on total pancreatic DNA content but not its negative effect on pancreatic weight, total pancreatic lipase activity, and RNA content (Fig. 11).

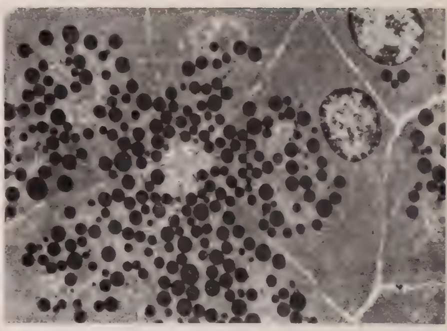
Discussion

CCK (7–12), its synthetic C-terminal octapeptide (11, 26, 27), and cerulein, analog of the C-terminal decapeptide of CCK (13–15), stimulate pancreatic growth.

CCK (28), the synthetic C-terminal octapeptide of CCK (27), and cerulein (14, 15) increase DNA synthesis and the DNA and RNA content of the pancreas; cerulein increases incorporation of labelled leucine into pancreatic proteins (29). The peptides exert hyperplasic and hypertrophic effects on the pancreas.

DL-ethionine, however, induces degenerative changes in the acinar parenchyma, interfering with protein synthesis (30), RNA (31), and phospholipid (32) metabolism. Ingestion of ethionine reduces the rate of enzymatic protein synthesis and reduces the discharge of enzymes from the pancreas, thus increasing the digestive-enzyme content of the gland in the first hours of ethionine ingestion (33). Ethionine reduces enzymatic discharge from the pancreas, for example, by blocking exocytosis (34). After ethionine ingestion is stopped, the pancreatic acinar parenchyma starts to regenerate after 11–12 days (35). However, when the concentration of peptides stimu-





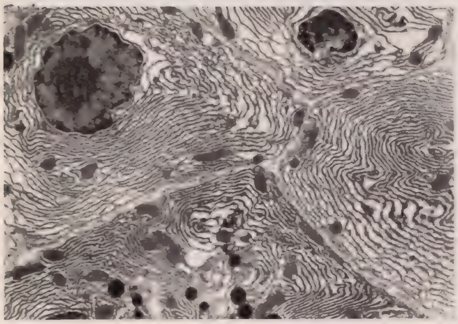


Fig. 8. Top left Electron micrograph of part of pancreas from CCK-treated rat; capillaries have enlarged diameters and contain many red blood cells (×6,240, moderately reduced).

Fig. 9. Top right Part of exocrine pancreas of control rat. Nuclei are small and circular, encircled by cisternae of granular endoplasmic reticulum. Mitochondria are located along lateral and basal borders, as elongated structures. A few pale vesicles appear at base, but very dense secretory granules appear in supranuclear region of cell. Microvilli project into irregularly shaped lumen; content of lumen of moderate density. (×6,600, moderately reduced).

Fig. 10. Left Electron micrograph of part of pancreas of ethionine-treated rat. Small, pyknotic nuclei are surrounded by dilated cisternae of granular endoplasmic reticulum (×76,760, moderately reduced).

lating pancreatic growth is kept at a high level in blood, as it was in our experiments, the toxic effect of ethionine in the pancreas cannot develop completely. This suggests that the regeneration process in pancreatic tissues runs almost parallel with the toxic effect.

Methionine also prevents ethionine's degenerative effect on the pancreas (2); a choline-deficient diet in combination with ethionine ingestion, however, aggravates the toxic effect on the pancreas, causing, in mice, acute hemorrhagic pancreatitis (31).

In our experiments, administration of CCK for 15 days increased pancreatic weight and DNA content. Cerulein increased pancreatic weight and DNA and RNA content; the RNA/DNA relation did not change. Both peptides increased the enzyme content of the pancreas; total pancreatic trypsin and total amylase activity increased, while lipase activity (13) remained unchanged. Both peptides exerted trophic effects on the pancreas.

In both experimental series, ethionine de-

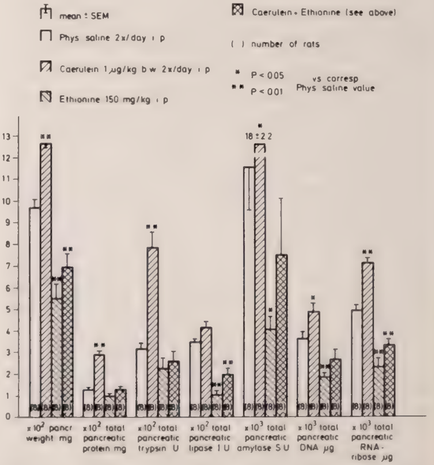


Fig. 11. Effect of intraperitoneal treatment with cerulein, ethionine, and cerulein-plus-ethionine (each for 15 days) on pancreatic tissue composition.

creased the weight of the pancreas, its DNA and RNA content, and amylase and lipase activity. It induced atrophy of the gland. CCK in combination with ethionine could not reverse ethionine's negative effect on total pancreatic DNA content. Cerulein did not counteract the effect of ethionine on pancreatic weight or on RNA and lipase content. Ethionine decreased the volume of pancreatic juice and amylase and lipase output in stimulated pancreatic secretions. Neither CCK nor cerulein could reverse these latter effects of ethionine, although CCK counteracted ethionine's depression of lipase activity. This is interesting in two ways. First, enzyme secretion from a damaged pancreas does not reflect the content of that enzyme in the gland. Second, ethionine decreases pancreatic lipase secretion, which reminds us of the steatorrhea of chronic human pancreatitis. Neither effect can yet be reversed sufficiently.

We conclude that neither CCK nor cerulein can completely repair damage to the pancreas induced by ethionine. CCK seems more potent in this respect than cerulein.

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Response of Plasma Norepinephrine Levels to Stimulation in Renovascular Hypertension

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Abstract

The role of the sympathetic nervous system in renovascular hypertension was assessed by comparing plasma norepinephrine (PNE) and plasma renin activity (PRA) levels in renovascular hypertensive, essential hypertensive, and normotensive subjects. Plasma sampling conditions included two sodium states (replete and deplete) and two body positions (supine and upright). Nonstimulated PNE and PRA were similar in the three groups. The stimulus of orthostasis increased PNE in patients with renovascular hypertension and mean stimulated PNE was higher (1045 pg/ml) in renovascular than in normotensive (573 pg/ml) or essential hypertension (551 pg/ml) ($p < 0.01$) patients, suggesting that increased sympathetic outflow may be partially responsible for the hypertension secondary to renal artery stenosis. There was no correlation between PNE and PRA in any of the study conditions. Relative hypovolemia in renovascular hypertension may contribute to the increased sympathetic outflow in patients with this condition.

The role of the renin-angiotensin system in renovascular hypertension (RVH) is well established. However, there is evidence that other mechanisms also participate in the maintenance of elevated blood pressure (1–5). Several reports have implicated the sympathetic nervous system in the onset and maintenance of experimental RVH in animals (6–12). Almost no information is available regarding the role of the sympathetic nervous system in human RVH (13, 14).

We have measured nonstimulated and stimulated plasma norepinephrine (PNE) in age-matched patients with RVH and with essential hypertension (EH) as well as in normotensive subjects (NT). Patients with RVH demonstrated a uniform and consistently greater increase in PNE in response to stimulation than did the other two groups, suggesting that increased sympathetic outflow may be partially responsible for the hypertension secondary to renal artery stenosis.

Materials and Methods

Experimental Subjects. There were three study groups: (a) 12 control subjects (NT); (b) 7 patients with mild to moderate EH; and (c) 7 patients with RVH. Other causes of secondary hypertension were ruled out by an appropriate clinical history, physical examination, isotope studies, intravenous pyelogram, and renal arteriogram (if indicated). The blood pressures of the 7 patients with RVH responded favorably to subsequent corrective operations. Antihypertensive and diuretic medications were discontinued and subjects were ingesting a regular salt diet (100 to 150 mEq sodium per day) for at least two weeks prior to the investigation. No women were taking oral contraceptives.

There were no demographic differences between groups. All subjects were white. Mean

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ages, in years, were: NT, 37.5; EH, 41.1; and RVH, 42.2. Male/female ratio was 6/6 in NT, 5/2 in EH, and 4/3 in RVH.

Study Design. Subjects underwent identical studies on two successive mornings. The study on Day 1 was conducted while subjects were sodium replete (sodium intake of 100 to 150 mEq per day verified by 24-hour urine collection). The study on Day 2 was conducted following the oral administration of furosemide, 1.2 mg/kg, at 5:00 PM of Day 1, followed by a restricted salt diet (10 mEq per day of sodium). As previously reported using the same protocol (15), there was no difference in weight loss or $U_{Na}V$ between the three groups following furosemide.

At 9:30 AM of Day 1, an indwelling catheter with obturator was inserted into an arm vein. Subjects remained undisturbed in the supine position in a quiet room for one hour. At the end of one hour, without subjects' awareness, a blood sample was drawn through the catheter for plasma renin activity (PRA), PNE, serum creatinine, and electrolytes. Patients then remained in the supine position for another 20 minutes, during which time blood pressures were recorded every two minutes with an automated ultrasonic device (Arteriosonde 1216, Roche Medical Electronics) (16).

Following one hour of ambulation with the indwelling catheter in place, the second blood sample was drawn for PRA and PNE. Blood pressures during ambulation were then recorded every two minutes for 20 minutes.

On Day 2, the same procedure was followed while subjects were in the sodium-deplete state. Blood samples for PRA and PNE were immediately placed in an ice bath and centrifuged in a refrigerated centrifuge, separated and frozen within one hour.

For each study subject, the blood pressures used for statistical analyses were the mean values derived from the ten pressure determinations over 20-minute periods in each of the four study states (supine and upright, sodium replete and sodium deplete).

Laboratory Methods. PRA was determined by a radioimmunoassay (17), as previously described from this laboratory (18). PNE was measured by a modification of the radioenzymatic technique of Peuler and Johnson (19).

Statistical Methods. The data were analyzed using a repeated measures analysis of variance model (20). The appropriate model included two experimental factors: sodium state (replete and deplete) and body position (supine and upright); and one grouping factor: etiology (normal controls, essential hypertension, renovascular hypertension). To stabilize the variance and transform the data to better conform to the assumption of normality, analyses of the PNE and PRA values were performed using the logs of the plasma concentrations. The calculations were accomplished using the general linear model procedure (PROC GLM) of the Statistical Analysis System (SAS) (21).

The antilogarithms of the means (thus geometrical means) and the relevant standard errors were computed (Table 1). To illustrate the effect of stimulus, we calculated the percent change due to stimulus for each patient (means and standard errors, Table 3).

Results

Baseline Values. Mean nonstimulated, control blood pressure (sodium replete, supine position) was 105/65 mmHg in the NT group, 159/102 mmHg in EH, and 156/101 mmHg in RVH. Mean nonstimulated, control PNE was similar in all three groups. PRA was higher in RVH than in NT and EH, although this difference was not significant. There was no correlation between systolic, mean or diastolic BP and PNE or PRA in any of the groups, nor was there a correlation between PNE and PRA.

Posture and Blood Pressure. In the sodium replete state, orthostasis (Table 2) resulted in a 5 to 8 mm rise in both mean systolic and diastolic pressures in NT and EH (not significant). RVH, however, demonstrated a decrease in systolic pressure of 13 mmHg ($p < 0.05$), with a slight increase in diastolic pressure similar to the other two groups. In the sodium deplete state, following the upright position the blood pressure did not change in NT, but in EH and RVH there was a decrease in systolic pressure of 20 and 23 mmHg ($p < 0.05$) and in diastolic pressure of 9 and 5 mmHg (not significant), respectively.

Sodium Depletion and Blood Pressure. In the supine position, sodium depletion (Table 2) did not significantly change either systolic or diastolic pressure in any of the groups. Following sodium depletion, the blood pressure in the upright position was lower than upright blood pressure in the sodium replete state in all three groups. This decrease was significant only for systolic pressure drop in RVH ($p < 0.05$) because of the consistency of response.

Posture and PNE. Mean PNE in the upright position was not significantly different in EH as

TABLE 1

Plasma Norepinephrine and Renin Activity (PRA) Levels in Normal Subjects (NT) and in Patients with Essential (EH) and Renovascular (RVH) Hypertension
(geometric mean ± SE)

	NT (N = 12)	EH (N = 7)	RVH (N = 7)
PNE pg/ml			
Supine sodium replete*	209 ± 16	210 ± 22	186 ± 19
Supine sodium deplete*	286 ± 22	254 ± 26	272 ± 28
Upright sodium replete†	374 ± 29	452 ± 47	624 ± 65
Upright sodium deplete‡	573 ± 45	551 ± 57	1045 ± 109
PRA ng/100 ml/3 h			
Supine sodium replete*	240 ± 31	287 ± 42	448 ± 66
Supine sodium deplete*	599 ± 58	502 ± 74	789 ± 116
Upright sodium replete*	441 ± 57	651 ± 96	1100 ± 162
Upright sodium deplete*	1492 ± 194	855 ± 126	2979 ± 437

* Differences between subgroups are not significant.

† RVH vs NT $p < 0.01$, RVH vs EH $p < 0.05$.

‡ RVH vs NT $p < 0.01$, RVH vs EH $p < 0.01$.

compared to NT in either the sodium-replete or the sodium-deplete state (Table 1). The absolute (Fig. 1) and relative (Fig. 1, Table 3) increase in PNE in response to orthostasis was slightly greater in EH than in NT (not significant). In contrast, the mean upright PNE in both sodium states was higher in RVH than in the other two groups ($p < 0.01$). The absolute and relative increase in PNE in RVH was approximately twice that in NT or EH.

Analysis of individual rather than mean PNE levels reveals that the RVH patients demonstrated a homogeneous response to upright posture, i.e., orthostatic PNE increased markedly in all patients in both sodium states (Figs. 2, 3). In contrast, the NT and EH groups showed marked variability.

Sodium Depletion and PNE. In separating the relative effects of the two stimuli used (upright posture, sodium depletion), we found that upright posture consistently increased PNE significantly more than did sodium depletion in the entire study population ($p < 0.01$), as well as within the three subgroups. The mean PNE rise attributable to sodium depletion in either the supine or upright position ranged from 31% to 83% (Table 3), and was not different among the three study groups. Analysis of individual patient responses to sodium depletion could distinguish no subgroups.

Posture and PRA. PRA increased in all study groups in response to upright posture. The mean PRA was higher during the sodium-deplete upright position in RVH than in the other two

TABLE 2

Blood Pressure Changes Following Upright Posture and Sodium Depletion
(arithmetic mean ± SE)

	Systolic Change (mmHg)			Diastolic Change (mmHg)		
	NT (n = 12)	EH (n = 7)	RVH (n = 7)	NT (n = 12)	EH (n = 7)	RVH (n = 7)
Upright Posture						
sodium replete	+8 ± 4	+8 ± 6	−13 ± 4*	+7 ± 3	+5 ± 4	+5 ± 3
sodium deplete	+1 ± 4	−20 ± 7*	−23 ± 5*	+1 ± 3	−9 ± 5	−5 ± 6
Sodium Depletion						
supine	−2 ± 3	−7 ± 9	−8 ± 4	0 ± 3	−3 ± 5	+2 ± 1
upright	−9 ± 4	−36 ± 15	−19 ± 2†	−6 ± 3	−17 ± 9	−8 ± 6

* Upright vs supine posture ($p < 0.05$).

† Sodium deplete vs sodium replete state during identical posture ($p < 0.05$).

TABLE 3

Relative Increase in PNE and PRA following Stimulation
(means of individual percent increase ± SE)

	Change in PNE (percent)			Change in PRA (percent)		
	NT (n = 12)	EH (n = 7)	RVH (n = 7)	NT (n = 12)	EH (n = 7)	RVH (n = 7)
A. Effect of Upright Posture						
sodium replete	101 ± 32	182 ± 42	248 ± 42*	110 ± 40	212 ± 53	180 ± 53
sodium deplete	108 ± 32	136 ± 42	308 ± 42*	192 ± 40	83 ± 53	324 ± 53†
B. Effect of Sodium Depletion						
supine posture	46 ± 17	31 ± 22	55 ± 22	243 ± 53	196 ± 69	104 ± 69
upright posture	73 ± 17	37 ± 22	83 ± 22	365 ± 53	68 ± 69	220 ± 69

* RVH vs. NT or EH $P < 0.01$

† RVH vs. EH $P < 0.01$ RVH vs. NT $P = 0.06$ (N.S.)

groups; however, this was not significant. This higher value in RVH reflects a consistent increase in PRA in all RVH patients in response to dual stimuli of sodium depletion and orthostasis. These same stimuli evoked a more variable response in EH, in which three patients had a minimal rise and four others had PRA responses similar to the RVH group (Fig. 2); the lower mean PRA in EH is attributable to the three low-renin patients. Only one patient in the EH group (EH-2, Table 4) demonstrated nonresponsiveness of both PRA and PNE to the combined stimuli of sodium depletion and upright posture.

Sodium Depletion and PRA. In the supine position, the absolute and relative rise in PRA following sodium depletion is similar in NT and RVH; an apparent smaller PRA increase in EH is attributable to the three patients classified as low-renin essential hypertension. As discussed above, the combined stimuli of sodium depletion and upright posture caused a dispersion of EH patients into low, normal and high renin categories.

The two stimuli, upright posture and sodium depletion, had equivalent effects on PRA (Table 3).

There was no correlation between control or stimulated PNE and PRA in the entire study population or within subgroups (Table 4), nor did control blood pressure or changes in blood pressures correlate with either PNE or PRA.

Discussion

Nonstimulated mean PNE and PRA were similar in age-matched subjects who were normotensive and had essential hypertension or renovascular hypertension. Two types of stimuli were used: furosemide-induced sodium depletion and upright posture. The effects of these two stimuli were analyzed separately and combined.

The stimulus of furosemide-induced sodium depletion was potent enough to result in anticipated increases in PRA in all three patient groups (22, 23), but caused only marginal increases in PNE. The stimulus of orthostasis, on the other hand, resulted in a much greater rise of PNE than did sodium depletion in all study groups. Previous studies have also shown that orthostasis is a more powerful stimulus for PNE than is moderate so-

TABLE 4

Comparison between PNE and PRA in Individual Subjects

		Nonstimulated		Upright, Na depleted	
Diagnosis & Pt. No.		PNE (pg/ml)	PRA (ng/100 ml/3h)	PNE (pg/ml)	PRA (ng/100 ml/3h)
EH	1	246	878	234	1091
	2	120	132	261	146
	3	122	188	354	3849
	4	276	216	712	361
	5	180	230	868	2731
	6	322	164	1044	428
	7	308	903	1100	1238
RVH	1	127	133	584	3638
	2	187	3050	748	8667
	3	142	312	796	2070
	4	363	311	1020	3124
	5	205	289	1022	1969
	6	244	643	1370	4270
	7	126	492	2734	1197
NT	1	147	577	221	2628
	2	67	60	283	62
	3	83	189	333	3224
	4	443	150	497	921
	5	186	143	549	1223
	6	190	247	574	893
	7	169	82	668	1528
	8	167	64	729	779
	9	135	317	769	3109
	10	480	2209	775	5370
	11	952	133	942	1190
	12	316	2209	1410	9773

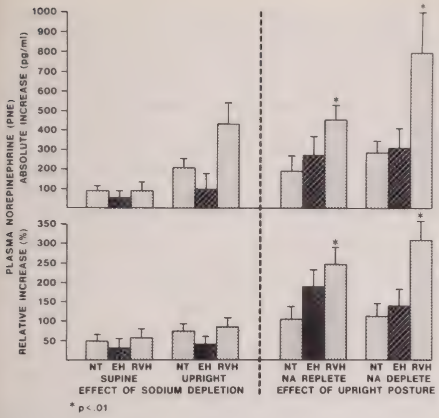

Fig. 1. Relative effects of sodium depletion and upright posture on plasma norepinephrine (PNE) in normotensive subjects (NT) and in patients with essential (EH) and renovascular (RVH) hypertension. Effect of sodium depletion calculated as differences in mean PNE between sodium-deplete and sodium-replete states. Effect of upright posture calculated as differences in mean PNE between upright and supine posture. Difference expressed as both absolute mean PNE increase ±SE (upper half of figure) and relative mean increase ±SE (lower half of figure).

dium depletion in normotensives and in patients with essential hypertension (24–28).

In the present study, mean PNE was not different between NT and EH in control or in stimulated states. This is in agreement with some reports (29–34) but not with others, which have shown higher mean PNE in EH than in NT (35–38). Goldstein (39) analyzed 32 published studies comparing PNE concentrations in EH and NT patients, the majority of which reported higher levels in the hypertensive group. He attributed much of the disparity in results to improper statistical analyses, varying assay techniques, and differences in ranges for normal PNE values, and pointed out that almost one-half of the studies purportedly showing a higher mean PNE in EH than in NT did not, in fact, show a statistically significant difference between the two groups; that is, only a trend was described.

Our data suggest that analysis only of mean PNE levels in groups of patients with NT or EH may partially explain the differences in previous reports because of marked variability of PNE in EH. Although the PNE values in EH in this study all fell into a narrow range in the nonstimulated state, orthostasis, regardless of sodium state, resulted in variable PNE responses: three of the seven EH patients had little or no rise in PNE, whereas the other four showed a clear and significant increase. Thus, during a dynamic stimulus to sympathetic outflow, patients with EH demonstrated a wide range of PNE responsiveness. This is reminiscent of plasma renin activity (PRA) in EH, where the stimulus of sodium depletion disperses individual patients into categories of low-, normal-, or high-renin hypertension (40), so that the mean stimulated PRA level for all patients with EH is of little physiological or clinical value.

In agreement with some previous reports (41–43), but not with others (22, 44–46), we found no individual or group correlation between PNE and PRA in the EH patients, that is, PRA and PNE were unrelated regardless of body position or sodium state.

Although our relatively small study group does not permit subclassification of EH into PNE responders and nonresponders, other researchers have reported subgrouping of PNE values in EH in the unstimulated or stimulated state (14, 26, 47). We critically reviewed prior publications in an attempt to ascertain whether PNE response to orthostasis and/or sodium depletion in patients with EH conformed to a bimodal pattern, as suggested by our results. All previous studies reported only group values; when data were presented in figures, it was impossible to track individual patient responses from nonstimulated to

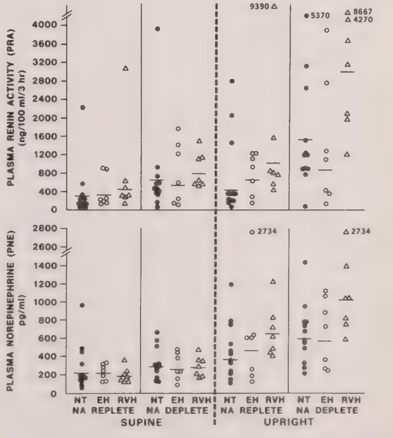

Fig. 2. Plasma norepinephrine (PNE) (lower half of figure) and plasma renin activity (PRA) (upper half of figure) in normotensive subjects (NT) and in patients with essential (EH) and renovascular (RVH) hypertension.

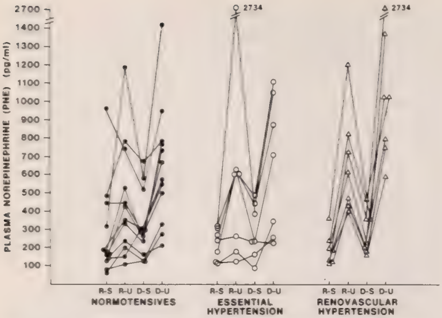

Fig. 3. Individual patient response of plasma norepinephrine (PNE) to upright posture. Abbreviations: sodium replete, supine posture (R-S); sodium replete, upright posture (R-U); sodium deplete, supine posture (D-S); sodium deplete, upright posture (D-U).

stimulated states. The PNE values from our larger group of NT subjects distributed more evenly about the mean level following stimulation. The suggested bimodality of PNE response to stimulation in EH, if it is eventually confirmed in a larger series of patients, suggests possible differences in pathogenesis and perhaps therapy of hypertension in PNE responders and nonresponders. A physiological subgrouping is described in a study of 37 patients with EH, in whom eight demonstrated defective neuronal uptake of norepinephrine (48). In a recent analysis of the literature, Goldstein suggested a subgrouping of PNE responses to the stimulus of exercise among patients with EH (49).

In contrast, the patients with RVH were a much more homogeneous group. In response to orthostasis, all seven patients were PNE responders. PNE levels in response to orthostasis in RVH were not different than those of the EH "PNE responders," although the relative rises tended to be greater.

These data suggest that PNE, or by implication increased sympathetic outflow, may be partially responsible for the maintenance of hypertension secondary to renal artery stenosis. There are no previously reported studies of PNE in clinical RVH. Januszewitz (13) reported higher urinary vanillyl mandelic acid secretion in RVH than in EH. DeQuattro (14) noted normal supine unstimulated PNE in four patients with renal artery stenosis, none of whom exhibited clearly lateralizing differential renal vein renin ratios.

In experimental RVH, Nishimura (6) showed elevated PNE levels in one-kidney, one clip (1-k, 1-c) and in two-kidney, one clip (2-k, 1-c) renovascular rats, whereas Dorr (9) found high PNE only in the 1-k, 1-c model. The role of the sympathetic nervous system in the 2-k, 1-c model, the experimental model most resembling human RVH, is still controversial. Dargie (50) concluded that the sympathetic system has no role in 2-k, 1-c RVH. No inhibitory effect of 6-hydroxydopamine (6OHDA) on the development of hypertension was reported by Provoost (51) after subcutaneous administration, or by Dragie (52) and Dorr (9) after systemic administration. Grewal (53), however, prevented RVH by 6OHDA in weanling but not in adult rats.

It is probable that both the sympathetic and renin-angiotensin systems participate in experimental renovascular hypertension. Inhibition of one system causes only partial reduction of the hypertension; inhibition of both systems is needed to normalize blood pressure. Gavras (54) arrived at this conclusion by using angiotensin converting enzyme inhibitor (CEI) in 2-k, 1-c RVH rats; CEI caused the same magnitude of BP reduction in both groups, but only the animals pretreated by alpha and beta blockade became normotensive. Similar conclusions were reached by Antonaccio (10) using combinations of CEI, 6OHDA and adrenal medullectomy. Zimmerman (55) demonstrated in 2-k, 1-c RVH dogs that guanethidine and saralasin were additive in BP reduction, and that both were needed to normalize BP.

What is the mechanism of high-stimulated PNE in RVH? Angiotensin II is known to facilitate norepinephrine release (56). It is generally held that the renin-angiotensin system plays an important role in RVH (57, 58), and we previously showed that RVH patients demonstrate greater secretion of renin than patients with EH in response to sodium depletion alone and sodium depletion combined with saralasin (33, 59). Therefore, it is possible that the high-stimulated PNE in RVH is partially caused by A-II facilitation. Increases of PNE, however, may occur independent of the renin-angiotensin system. Gavras (54) reported that PNE in RVH was not suppressed by administration of CEI. Nishimura (6) found that the rise in PNE following hemorrhage was not affected by CEI. In the present study, there was no correlation in RVH between PNE concentrations or changes and those of PRA. Furthermore, the magnitude of changes in PNE and PRA differed in response to the two stimuli. Sodium depletion caused a significant increase in PRA with only minimal changes in PNE.

In this study, upright posture in the sodium-deplete state resulted in a marked drop in systolic blood pressure in RVH, but not in NT or EH. Clinically, this suggests that RVH subjects were relatively hypovolemic compared to the subjects with NT or EH. It has been shown that plasma volume is lower in RVH than in patients with mild or moderate EH (60). The supernormal rise of PNE in response to the upright position in RVH may therefore be partially mediated by increased sympathetic outflow in response to a hypovolemic-induced drop in systolic pressure. In any event, the difference in PNE in the upright posture suggests increased sympathetic outflow in RVH over EH in response to this stimulus.

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Dose-Related Nephrotic Syndrome in Penicillamine-Treated Rheumatoid Arthritis

HARRY SPIERA, M.D.

Penicillamine is a long-acting agent for the treatment of rheumatoid arthritis. Its use is limited by substantial toxicity, including nephrotoxicity (1). Reported here is a case of rheumatoid arthritis initially controlled with 125 mg of penicillamine but in which, within 48 hours of increase of the dose to 250 mg, an acute nephrotic syndrome developed which subsided quickly after the penicillamine was discontinued. Subsequently, owing to a flare-up of the rheumatoid arthritis, the patient was started on only 50 mg of penicillamine a day and once again had remission of the disease without recurrence of proteinuria.

Case Report

A white male patient developed rheumatoid arthritis at age 29 and was treated with corticosteroids by a general practitioner with only partial control of the disease. When first seen by the author 3 years later, the patient had active rheumatoid arthritis involving his shoulders, elbows, wrists, knees, and ankles. He had subcutaneous nodules but no stigmata of Sjögren's syndrome or vasculitis. The sedimentation rate at that time was 43, latex fixation test was positive in a titer of 1:10,240, and antinuclear antibody was negative. The patient's urinalysis was normal.

Gold therapy was begun, and for a period of time the patient had an excellent response with a tapering of prednisone to 7-½ mg a day. He remained on the maintenance gold for 3 years, and then the rheumatoid arthritis exacerbated and he was given a second course of gold over a period of 6 months. The clinical course remained intermittently active for about 2 more years, at which time he developed septic arthritis that responded to treatment. He subsequently developed vasculitis of the fingertips and biopsy-proven interstitial pulmonary fibrosis. The latter responded to azathioprine given over a period of 6 months. Azathioprine was discontinued in 1975.

The patient's condition remained stable on 5–10 mg of prednisone until early 1977, when his arthritis flared up and he was begun on penicillamine, 250 mg/day. At the time the penicillamine was begun, the urine was free of protein. However, because of stomatitis and decrease in taste sensation, penicillamine was discontinued. The arthritis gradually became much worse, and penicillamine was reintroduced at 125 mg/day.

The patient remained relatively well for the next 2 years on that dose combined with 5 mg of prednisone a day. He was seen on October 1, 1981, for a flare-up of rheumatoid arthritis as manifested by acute synovitis in multiple joints; the sedimentation rate was 60 mm/hour. On that day no protein was noted in the urine. Penicillamine was increased to 250 mg/day, and over the next few days the patient had a marked weight gain and generalized edema.

He was admitted to The Mount Sinai Hospital on October 12, 1981. At that time he had anasarca, ascites, bilateral pleural effusions, and 4+ pedal edema. Creatinine was 1.1 mg%, albumin was 1.6 gm%, and cholesterol was 388 mg%. Urinalysis disclosed 4+ protein, with two to three red cells per high-power field, and the 24-hour urine protein was 12.2 gm. The antinuclear antibody was negative. C_3 and C_4 were normal. No

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kidney biopsy was done. Penicillamine was discontinued, and prednisone was increased to 20 mg/day. Hydrochlorothiazide was given to control the edema.

On October 26, 1981, the edema had disappeared, the urine was negative for protein, and the albumin had risen to 2.7 gm/dcl. The cholesterol was 436. The urine continued to be free of protein, and by January 20, 1982, the albumin was up to 4.4 gm%. Subsequently there was a progressive flare-up of rheumatoid arthritis, and by March 1982, the patient was once again severely disabled in spite of being on 10 mg of prednisone a day.

On March 29, 1982, with consultation and informed consent, he was once again started on 50 mg of penicillamine a day (supplied by I. A. Jaffe) with daily monitoring of the urine with Albustix. By November 2, 1982, the rheumatoid disease was once again in remission on 50 mg of penicillamine and 2 mg of prednisone a day. Albumin was 4.3 gm%, sedimentation rate was 42 mm/hour, and creatinine was 0.9 mg%. The rheumatoid arthritis has remained under excellent control, with no recurrence of proteinuria.

Discussion

The patient described was remarkable in that his disease initially came under excellent control with 125 mg of penicillamine, but within 48 hours of its being increased to 250 mg, he developed an overt nephrotic syndrome, which reversed after the penicillamine was discontinued. Subsequently with recurrence of rheumatoid activity he was once again begun on very small doses of penicillamine (50 mg/day), and the condition once again remitted without any apparent renal disease.

It has been suggested that the nephropathy induced by penicillamine is mediated by the immune complex. Evidence for this is the presence of IgG and complement in renal lesions associated with use of penicillamine (2). The dramatic response of the kidney disease to small alterations of penicillamine dose might bring this hypothesis into question. The dose of penicillamine necessary to induce a beneficial effect in the individual patient has not been clearly defined. Indeed, it seems to vary significantly from patient to patient.

I report experience with this patient to bring attention to the potential reversibility of the nephrotic syndrome induced by penicillamine. The case also raises the question of whether nephrotoxicity is a contraindication to continuing use of penicillamine in low doses when it has been shown to be effective. Much further work will be necessary to define these questions.

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Diagnosis of Polar Hypertrophy of the Kidney Revisited

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Abstract

Since 1973, a sign characteristic of polar hypertrophy of the kidney on intravenous pyelography or nephrotomography has been evaluated and proved consistently accurate without false positives or negatives. This sign consists of rounding and enlargement of a renal pole on the frontal (anteroposterior or posteroanterior) projection of the intravenous pyelogram, which then appears normal in shape and size on posterior ipsilateral oblique view with normal spatial symmetrical distribution of the calyces within the involved pole in both views. Diagnostic differentiation between polar hypertrophy of the kidney, a benign congenital hyperplasia, and neoplasms by intravenous pyelography is illustrated in four case reports.

Polar hypertrophy in a kidney represents a benign congenital hyperplasia localized to a single pole, which has at times been mistaken for neoplastic change. Such errors in differential diagnosis can be avoided, however, by observing the characteristic findings of the hypertrophy. These include symmetrical calyceal distribution in the involved segment and, more important, a normal-appearing renal pole on oblique intravenous pyelography (IVP) or nephrotomography (NTG) films, since the enlargement is in the transverse diameter rather than anterior-posterior. Computed tomography and arteriography can lend support to the diagnosis if necessary.

Case Reports

Polar Hypertrophy: Case 1. A 70-year-old woman admitted with angina pectoris, weight loss, and anorexia was investigated with IVP. This revealed rounding and enlargement of the superior pole of the right kidney with symmetrical spatial distribution of the collecting system within the involved pole of that kidney. The right posterior oblique view showed normal tapering of the upper pole of the kidney and symmetrical distribution of the calyceal system within the upper pole (Fig. 1).

Computed tomography showed increased transverse diameter of the upper renal pole compared to the ipsilateral lower pole, a finding best appreciated on the cathode ray tube (CRT) monitor. This monitor is a console on which the radiologist can display images, adjust window and level settings, and use software for reconstructions in coronal, sagittal, and diagonal planes (Fig. 2).

Polar Hypertrophy: Case 2. A 76-year-old man who had had bladder resection with ileal conduit was admitted with bleeding from his stoma and evaluated with an IVP. This demonstrated rounding of the upper pole of the right kidney in the AP projections that showed a normal tapered outline in the supine right posterior oblique projection, with symmetrical spatial distribution of the calyces in both views. This combination of findings is characteristic of polar hypertrophy. In addition there was duplication of the left collecting system and evidence of bilateral fibrolipomatosis (Fig. 3). Computed tomography of the retroperitoneal space revealed the transverse diameter of this pole to be greater than that of the lower pole (Fig. 4).

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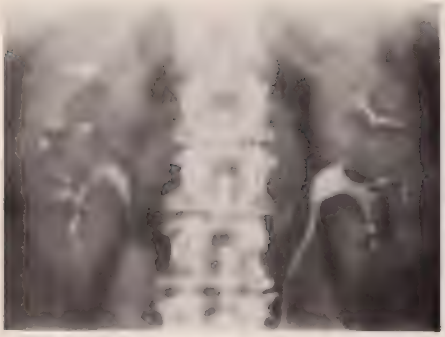


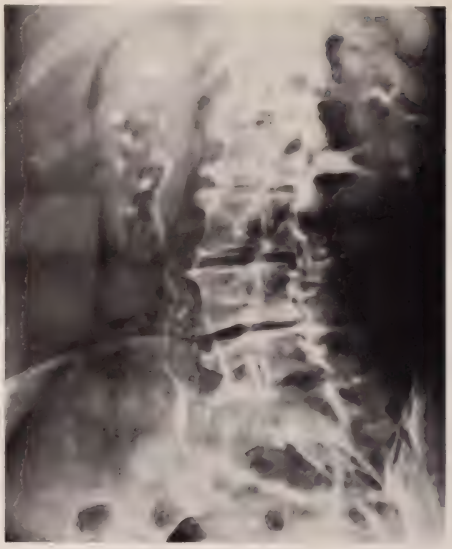


Fig. 1. Case 1. Five-minute film from IVP demonstrates unipolar hypertrophy of superior pole of right kidney (**left**). The right posterior oblique view (**right**) shows normalization of renal contour.

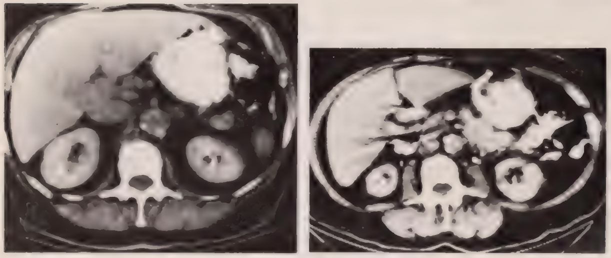
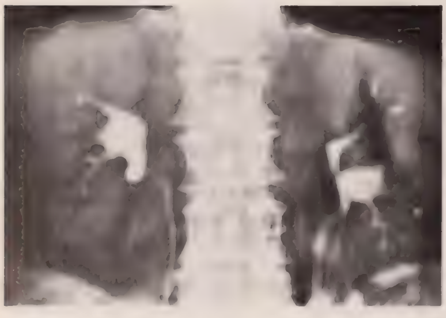


Fig. 2. Case 1. CT demonstrates no abnormal renal masses in superior or inferior poles, but discrepancy in transverse diameter of superior (**left**) and inferior (**right**) poles of right kidney.



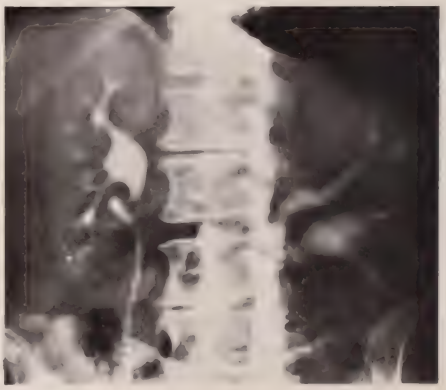


Fig. 3. Case 2. Frontal (**left**) and oblique (**right**) films of IVP demonstrate right superior pole hypertrophy, which appears normal on oblique view.

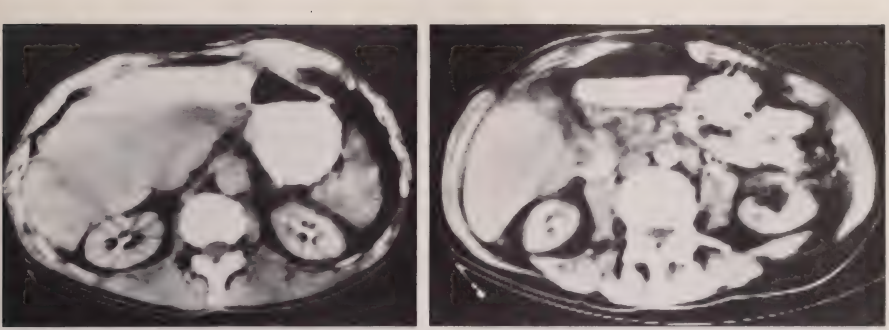


Fig. 4. Case 2. CT demonstrates asymmetry of transverse diameter of superior pole of right kidney (left) as compared to same pole of left kidney (right).

Neoplasms. In contradistinction to polar hypertrophy, renal masses tend to produce symmetrical or asymmetrical enlargement of the involved pole that persists in the anterior-posterior (AP) projection as well as the corresponding posterior oblique projection. Also present are an asymmetrical distribution of the calyces within the involved pole and, often, pressure defects of the calyces and/or amputation of one or more calyces from tumor involvement. Two cases illustrate these findings.

Neoplasms: Case 3. A 65-year-old man was admitted with microscopic hematuria and right flank pain of several months' duration. An intravenous pyelogram showed a 9.5 × 11 cm mass effect involving the lower pole of the right kidney with a lobulated margin, prominently noted on the AP and oblique views. The calyces were asymmetrically placed in relationship to the kidney margins in the AP as well as the supine right posterior oblique projections. This is a distinguishing feature of masses as opposed to polar hypertrophy in which the spatial distribution of the calyces in relationship to the kidney outline is symmetrical and normal in both the AP and corresponding posterior oblique projection. Upper ureteral displacement was also observed (Fig. 5).

Angiography revealed evidence of a large renal mass in the lower pole of the right kidney with neovascularity and lucent defects consistent with necrotic foci (Fig. 6). Pathology proved renal cell carcinoma of the mixed clear and granular cell types.

Neoplasms: Case 4. A 66-year-old woman admitted with right upper quadrant pain was investigated with IVP. This showed right upper

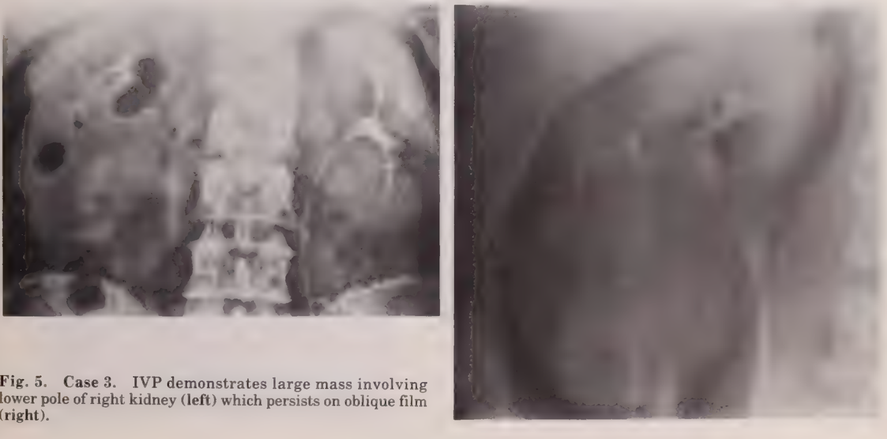


Fig. 5. Case 3. IVP demonstrates large mass involving lower pole of right kidney (left) which persists on oblique film (right).

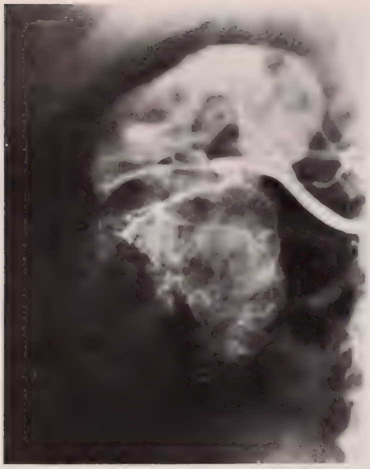


Fig. 6. Case 3. Angiography reveals neovascularity at site of tumor mass.

pole enlargement associated with an enlarged, lobulated contour and calyceal displacement suggestive of a space-occupying lesion (Fig. 7). Angiography demonstrated tumor vascularity. Pathology confirmed clear cell carcinoma (Fig. 8).

Discussion

The concept of polar hypertrophy was first reported in 1968, and hypothesized to be due to congenital hyperplasia of the kidney localized in one of the renal poles (1).

In 1972 one of us (LOM) made the observation of this sign that was presented in a paper at the Commemorative Congress—Fortieth Anniversary of the Mexican Academy of Surgery in Mexico City, Mexico (2). Since then we have followed over 35,000 cases and to the best of our knowledge, we have not had any false positives or false negatives. Our radiologic observations were correlated with either (a) follow-up examinations or (b) angiography, and later on (c) computed tomography, after this modality was introduced as a diagnostic tool. This sign has survived the test of time. Ultrasound correlations performed in several of our patients show no evidence of a tumor mass, since polar hypertrophy is nothing but renal parenchyma growing preferentially in a transverse fashion in a pole of the kidney.

Pyelography in these polar hypertrophy patients shows positive findings (3). One way to distinguish neoplasm is by computed tomography, which shows no mass; another is by arteriography which shows normal vascularity of the involved pole. Based on eleven years of experience gained at Mount Sinai Medical Center of Greater Miami with IVPs and nephrotomography, angiography, and more recently, CT, our impression is that polar hypertrophy has two characteristics whereby the differential diagnosis from neoplasms can be established in the majority of cases:

First, conventional IVP shows symmetrical

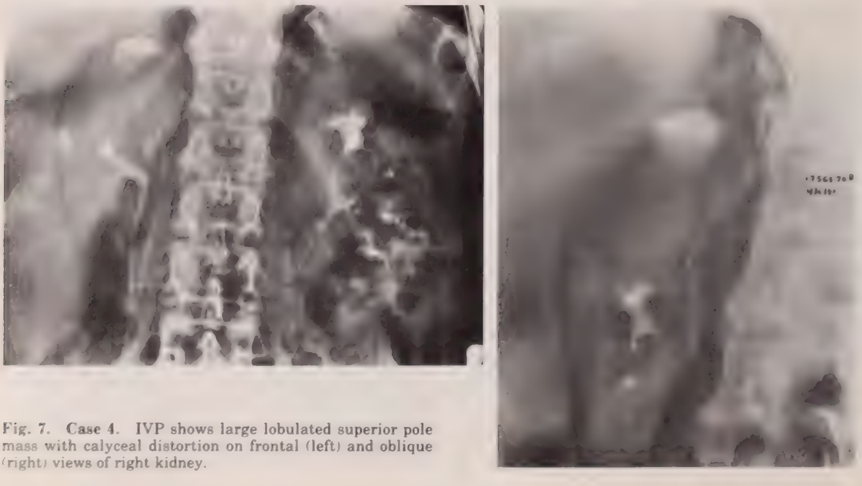


Fig. 7. Case 4. IVP shows large lobulated superior pole mass with calyceal distortion on frontal (left) and oblique (right) views of right kidney.

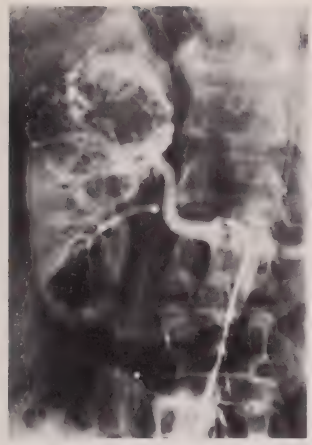


Fig. 8. Case 4. Angiography demonstrates minor vascularity.

spatial distribution of the calyces in the involved pole, with equidistant placement of these calyces from the renal margins.

Second, polar hypertrophy is seen in the supine and prone views. However, when the patient is placed in the posterior oblique position of the involved side, the superior or inferior pole (whichever the case may be) which appeared enlarged in the supine and prone views tapers off and shows a normal outline.

In this type of congenital hyperplasia, the enlargement seems to be at the expense of the transverse diameter, but not the anterior-posterior. This differs from that which occurs in neoplasms, where the growth is in all directions, as shown in Cases 3 and 4. Computed tomography confirms the lack of a mass in polar hypertrophy and shows increased transverse diameter of the involved pole compared to that of the other ipsilateral pole. This is best appreciated by use of careful analysis and reconstructions by the CRT monitor. Naturally, when in doubt, arteriography will make the diagnosis (4–6).

In summary: IVP is a simple, fast method to differentiate polar hypertrophy from a renal mass. The characteristic signs described are consistent to the extent that in most cases it is unnecessary to do CT or angiography to rule out a mass.

Acknowledgments

We thank Jan Holle for her assistance in editing this paper.

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Surgical Management of Duodenal Duplication Cyst Simulating Pyloric Stenosis

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Abstract

A cystic duplication of the duodenum represents a rare congenital anomaly which may simulate idiopathic hypertrophic pyloric stenosis. In the case reported here, postprandial vomiting and a palpable abdominal mass prompted a misdiagnosis of pyloric stenosis until celiotomy was performed. Although radiographic and endoscopic procedures would distinguish between these two diagnoses, a child who offers a "classical" clinical presentation of pyloric stenosis need not undergo further preoperative evaluation. But, as illustrated, duodenal duplication cyst should be considered in a differential diagnosis.

Whether anticipated or unexpectedly encountered intraoperatively, appropriate surgical management of duodenal duplication cyst depends upon the surgeon's familiarity with the diagnosis and the location of the cystic duplication.

Duodenal duplication was first reported in 1880 by Sanger (1) in a stillborn girl with multiple congenital anomalies. In 1965, Inouye (2) was the first to report a preoperative diagnosis of duodenal duplication. A rare lesion, it is seldom considered in the differential diagnosis of patients presenting with vomiting and abdominal mass (3). Leenders (4) was able to collect only 50 cases from the international literature. A wide variety of therapeutic procedures have been proposed, several of which have fallen into disfavor.

This paper underscores the facility with which cystic duodenal duplication may, in large measure, clinically simulate pyloric stenosis (5, 6). An approach to the surgical management of such a cyst is proposed.

Case Report. A six-week-old white female infant was well until two days before admission to the hospital, when she twice vomited nonbilious material after eating. Substitution of sugar-flavored water for formula was tolerated for a day. Then, full strength formula feedings were resumed. However, vomiting returned, postprandial and projectile in nature, consisting first of milk and gastric content and then of bile-stained material. Emesis was nonbloody and stools were normal; there was no weight loss and no history of congenital anomaly in the family.

Physical examination revealed a nontender, firm, mobile mass, 2.5 cm in diameter in the right upper quadrant of the abdomen. Stool was guaiac negative. Nasogastric decompression yielded cloudy, grayish gastric contents. A complete blood-cell count, urinalysis, and analysis of serum electrolytes yielded normal values.

After intravenous hydration, the following day, the patient was operated upon with a preoperative diagnosis of idiopathic hypertrophic pyloric stenosis. At operation, only a slight thickening of the pyloric channel was observed. There was slight proximal duodenal dilatation and some distal diminution in duodenal caliber. In addition, an intrinsic duodenal mass was noted, 1.5 cm distal to the pyloroduodenal junction. Further exploration revealed no other pathology. A longitudinal duodenotomy exposed the mass, a cystic

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structure, 2 cm in diameter, intimately adherent to the superior, lateral, and anterior aspects of the first and second portions of the duodenum (Fig. 1). The papilla of Vater was positioned along the mid-portion of the cyst's medial wall. Upon unroofing the cystic structure along its anterior portion, clear mucoid fluid was evacuated (Fig. 2). No communication with the duodenal lumen was identified. Pathologic section of the excised portion confirmed duodenal mucosa and fibromuscular tissue. A duodenoplasty was performed, closing the duodenotomy transversely. Subsequently, an isoperistaltic retrocolic gastrojejunostomy was fashioned. The nasogastric tube freely drained bilious material.

On the first postoperative day, the patient was febrile to 102°F. A small suture-line collection was evacuated and intravenous antibiotics were given, with complete resolution of the infection. Peripheral hyperalimentation was maintained until the ninth postoperative day, when oral feedings were given, progressing to the infant's regular diet.

Since discharge, followup has shown the infant's course to be uneventful with satisfactory weight gain and gastrointestinal function.

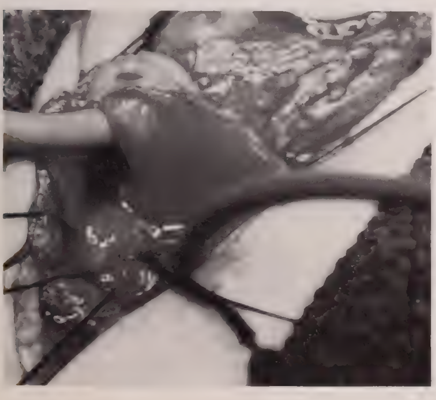
Discussion. Duodenal duplication is a rare congenital anomaly. As in the case reported, it is usually spherical. It may project intraluminally or extraluminally, usually in a posteromedial position, commonly from the first or second portion of the duodenum.

The duplication shares a common blood supply and muscularis with the duodenum. The mucosal lining in most cases is of duodenal origin, but it may contain ectopic gastric tissue, as in 15% of cases (7), or pancreatic tissue, or other intestinal tissue. The cystic fluid may appear either clear or maroon when associated with pressure necrosis and hemorrhage. Its consistency varies from watery to mucoid.

A duplication in the second portion of the duodenum may communicate with the biliary tract and may even be buried within the pancreas. A tubular duplication may communicate with the duodenal lumen, usually at one end. Duodenal duplications have been reported to measure 2 cm to 12 cm in greatest dimension and may be single or multiple (2). They are easily distinguished from mesenteric cysts, which lack the common muscular wall and mucosal lining.

Duplications are usually symptomatic in infants and children below the age of four months. Males and females are equally affected. Vomiting, high intestinal obstruction, and palpable abdominal mass should suggest this diagnostic possibility. The vomitus is usually not bile stained, except in the instance of rare periampullary or infraampullary obstruction, as observed in this case. Hyperacidity from ectopic gastric mucosa may lead to peptic ulceration, with risks of gastrointestinal hemorrhage with hematemesis and perforation (7, 8). However, massive melena has not been reported in association with duodenal duplication cysts (9). Duodenal duplication has also been implicated in the production of pancreatitis (10).

The clinical presentation of duodenal duplication cysts in large measure may simulate pyloric stenosis. The case presented here appeared classical for idiopathic hypertrophic pyloric stenosis, particularly with the history of progressively pro-



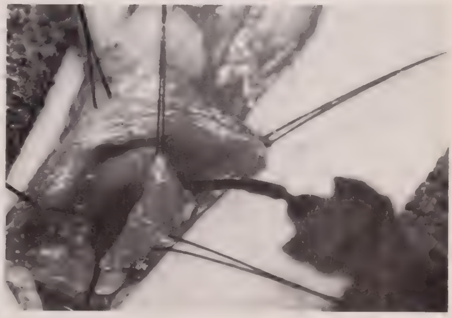


Fig. 1. Left Duodenal duplication cyst.

Fig. 2. Right Duodenal duplication cyst unroofed.

jectile postprandial vomiting and the physical finding of the "pathognomonic olive-shaped" abdominal mass in a previously asymptomatic infant six weeks old. Although the vomitus of pyloric stenosis is typically nonbilious, it, rarely, may contain bile that has refluxed into the stomach.

Our practice has been to operate without further diagnostic evaluation in infants presenting with a history and physical examination that are consistent with pyloric stenosis. An upper gastrointestinal series and endoscopy would distinguish this from duodenal duplication easily (11) but are felt to be unnecessary in pyloric stenosis, the more common condition.

The literature offers a variety of surgical treatments for duodenal duplication. Marsupialization (12), external drainage (6), and aspiration (5) have fallen into disfavor, as they offer no cure. Several procedures, however, have been successful. The lesion encountered in our patient was small enough to be treated with a modified "window" operation involving the excision of the wall between the cyst and the duodenal lumen, as originally proposed by Gardner (13). Since the papilla of Vater was located in the center of the medial wall of the cyst, complete excision in this instance was precluded. These duplications usually share a common blood supply with the juxtaposed duodenum; consequently, excision of the entire cyst would jeopardize the vascular supply to the remaining duodenal wall. Duodenoduodenostomy or duodenojejunostomy were not feasible as the obstructing lesion was located only 1.5 cm distal to the pyloroduodenal junction. Cystojejunostomy was not chosen because of the small size of the cyst and the precarious proximity of the papilla of Vater (2, 3). A gastrojejunostomy was deemed necessary to alleviate the possibility of a recurrent obstruction, should the cyst eventually refill.

Thus, the operation performed for duodenal duplication cyst must be tailored to the size and location of the cyst, with attention to the exact location of the papilla of Vater.

Although the diagnosis of duodenal duplication cyst should be considered as a possibility in the differential diagnosis of the vomiting infant, endoscopic and/or radiographic examinations are not necessary if the "pyloric" mass is palpated. However, in face of a history of bilious vomiting, either of these examinations is indicated.

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Synovial Sarcoma of the Anterior Abdominal Wall

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Synovial sarcoma very rarely may arise from extrasynovial tissue (1). An uncommon origin of synovial sarcoma is the anterior abdominal wall, where diagnosis of the nature of the mass is unlikely to be made preoperatively (1, 2).

Case Report. A 15-year-old boy presented with a large, right upper quadrant mass of four months' duration. There was no history of weight loss or constitutional symptoms.

Physical examination was unremarkable with the exception of a palpable, flat, nontender mass, 15 cm in diameter, occupying the right upper quadrant and extending to the right flank.

Routine laboratory tests revealed no abnormalities. Urinary VMA and HVA levels were within normal limits. Serum LDH, SGOT, SGPT, CPK, and alkaline phosphatase levels were mildly elevated.

Excretory urography demonstrated normal-sized kidneys without displacement. The mid-portion of the right ureter was displaced antero-medially by a large soft tissue mass. Faint calcification was noted within the mass (Fig. 1). The right psoas line was not visualized. No bone abnormalities were noted.

Chest radiographs and computed tomography of the chest were normal. A bone scan demonstrated no abnormalities.

A barium-enema examination demonstrated no intrinsic cecal or colonic abnormalities, although there was mild displacement of the sigmoid loop to the left.

An exploratory laparotomy was performed. A soft tissue mass with prominent surface vessels was found arising from the transversus abdominis muscle. The mass was covered by smooth peritoneum and there was no invasion of surrounding structures. The tumor was resected en bloc with peritoneum, transversalis fascia, transversus muscle, and a portion of internal oblique muscle.

Histologic examination revealed typical features of synovial sarcoma with the characteristic mixture of two cell types, i.e., glandular formation and spindle cells (Fig. 2).

Discussion. Synovial sarcoma arising from the anterior abdominal wall is an extremely rare tumor, with only twelve cases reported (1, 2). Although synovial sarcomas arise commonly near joints, most frequently in the extremities, they may also arise from sites where synovia or bursae are not known to occur, such as the retropharyngeal space (3, 4) and the anterior abdominal and chest walls. The presence of preformed synovia is thus not prerequisite for the development of synovial sarcoma. It is postulated that these tumors arise from undifferentiated mesenchyme which has resumed the potential for synovial differentiation.

The usual age of presentation is young adulthood; however, a range from two weeks to 75 years has been reported (5). The patients are predominately male (6).

The most frequent presenting symptom is abdominal pain (7), although in many instances a mass has been noted to be slowly growing, as in our case where the patient was aware of the presence of the mass for some time without divulging this to his parents.

Because of the thickness and tension of the overlying muscles and abdominal skin, the tumor

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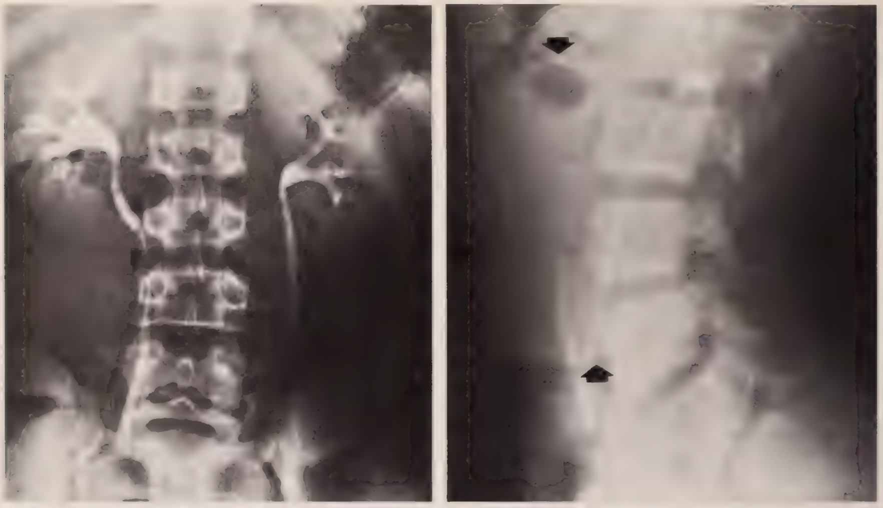

Fig. 1. Five-minute excretory urogram showing right mid-abdominal mass involving retroperitoneum, causing medial deviation of right ureter (arrow) with an element of obstruction (fullness of right upper collecting system and intensified right nephrogram). There is faint stippled calcification in mass. **Right** Lateral view shows extent of the tumor between the arrows.

grew inwards causing displacement of the bowel and even affecting retroperitoneal structures. This type of growth confused preoperative diagnosis and the tumor was thought to arise from intraperitoneal or retroperitoneal strictures (Fig. 1). It should be recognized that abdominal-wall tumors, including rhabdomyosarcoma, may exhibit such behavior. Synovial sarcoma, a very rare abdominal-wall tumor, may also extend internally and be confused with an intraabdominal mass.

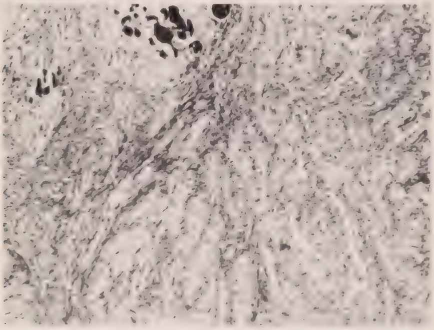

Fig. 2. Histologic appearance of tumor showing biphasic pattern consisting of glandular formations, clefts and spaces lined with columnar to cuboidal cells, and groups of spindle cells in between. Note (top, black) focal calcification (H&E × 100 moderately reduced).

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The Papago Indians: Historical, Social, and Medical Perspectives

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Abstract

This article synthesizes experience and knowledge gained from working with the Papago Indian tribe of southern Arizona. The history, culture, and traditional medical practices of the people are described. Both historical and contemporary health profiles are provided, with an emphasis on the current problem of diabetes mellitus. This disease affects 50%–70% of all adult Papagos and probably is caused by a complex interaction of environmental, genetic, and psychosocial factors.

The Papago people are an American Indian tribe who live in the Sonoran Desert in southern Arizona. The authors spent six weeks working among the Papagos in the Indian Health Service Hospital in the capital of their reservation, Sells. The reservation is roughly the size of the state of Connecticut and it is the ancestral home of the 14,000 tribal members. The people live in 74 small villages, only nine of which have a population greater than 100 persons. Living in virtual isolation from the twentieth century, the people are friendly and peaceful. They prefer a traditional way of life and still practice many of the customs passed down from their ancestors.

This paper describes the history and culture of the Papago tribe. Emphasis is placed on traditional concepts of health and healing. The contemporary health profile and disease patterns of the people are discussed. The problem of diabetes mellitus is focused upon to help the medical community gain a better understanding of the conflicts between the Indian and modern American ways of life.

History of the Papago

Archaeologists date the arrival of the Papago Indians into the Sonoran Desert some 10,000 years ago (1). The Papago are thought to have migrated from central Mexico because of the great similarities between Aztec and Papago language and religion. Especially interesting is that the main god of the two tribes has an almost identical mythology and Aryan appearance (2).

The early Papagos were hardly a tribe, since they moved about in many small groups. They wandered over vast areas of the American southwest, the borders of which were the Gila River in the north (home of the Pima Indians), the Chiricuhua Mountains to the east (home of the Apache Indians), and Mexico to the south (home of the Aztec Indians). The small groups of Papagos lived independently, maintaining different social and political structures but sharing a common language. Their land was entirely desert; unlike their neighbors, the Pimas, they had no reliable source of water.

Forced to adapt to a dry and harsh climate, the Papagos evolved a cyclical pattern of seasonal migration. During the winter months the people lived in the mountains in small villages near springs or wells. They hunted local wildlife and ate the crops stored the previous summer. Even so, food was scarce and survival was an everyday problem. When the desert bloomed in the late spring, the Papagos would move down to the desert floor. Here they would locate themselves near "arroyos," the peculiar desert streams produced by sudden rainstorms. Crops of corn, beans, and squash were strategically planted to benefit from the rapidly flowing streams. Water was also

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stored in manmade pools called "charcos," which were sometimes a few acres in size and can still be seen today in the desert. Despite the scorching summertime heat, the Papagos were blessed with an opulent desert flora of beautiful cacti such as the majestic saguaro, the prickly pear, and the cholla. During the summer months the cacti were prolific bearers of delicious and nutritious fruits, a staple in the Papago diet. The juices of the fruits were also used to make potent wines used in religious ceremonies.

Although the Papagos were well adapted to the dry desert climate, in extremely harsh years they were forced to move to the Gila River in the north. There they stayed with the Pima Indians, to whom they bore a resemblance and with whom they shared similar customs.

When the seasonal rains abated in October, the charcos and arroyos would become dry and again the Papagos would make their annual ascent to their winter villages in the mountains. They would pack up their grains and other crops grown during the summer and store them in large ornamental baskets woven by the women.

The life of these peaceful desert people remained uninterrupted until the arrival of the Spanish in the 1600s. The Spaniards caused significant changes in the Papago way of life through the introduction of domesticated animals and better techniques of farming. The net result was a greater supply of food, increased mobility, and less reliance on the traditional social structure which focused on the family and village. The Spanish also introduced Christianity to the Papago people, making them the first converts among the American Indians in the New World (3). Under the influence of a Jesuit priest, Father Kino, the Papagos became devout Christians. Even so, the people did not abandon their own gods but developed a unique blend of religions, in effect adding another god to their pantheon.

While under Spanish rule in the late 1700s the Papagos became prey to the warring Apache tribe. The raids necessitated cooperation among the many small Papago groups, which resulted in the emergence of a unified tribal structure in the early 1800s.

Although the Papagos are legendary for their acquiescent and peaceful nature, they became fierce warriors when required to defend their families and property. They were known to carry 100 arrows at a time and were extremely agile with wooden clubs. Their customs related to killing an enemy in a war are interesting. A Papago warrior who killed an enemy was required to stop fighting but remain on the battlefield, blackening his face and remaining quiet. The enemy found this practice rather puzzling and would not harm such a bystander. When all the Papago warriors returned to their village, those who had slain an enemy were considered unclean; for 16 days, these warriors would remain isolated in order to purify their bodies (4).

The Papagos remained under Spanish (and later Mexican) jurisdiction until 1853, when their lands were obtained by the U.S. Government in the Gadsden Purchase. Approximately a third of the tribal land remained in Mexico by that agreement. This left many Papagos in Mexico, where they live today. After the Gadsden Purchase, non-Indians began to filter onto the Papago territory, claiming much of the grazing land, digging gold mines, and disrupting the Papago way of life.

In 1882, the land upon which the Papagos had lived since 8000 BC was formally secured by an act of Congress. The tribe received a reservation totalling 2.85 million acres, a mere fraction of their original tribal lands. The size of the reservation was determined by the inclusion of all land from which Baboquivari Peak a mountain holy to the Papagos, could be seen. They were the last American Indian tribe to be given a reservation and were also the last tribe to receive the rights to all of their mineral holdings (in 1955). Despite their right to exploit the natural wealth of the land, the Papagos have yet to exercise it. This would require a great deal of capital and greater contact with the Anglo world, both of which the Papagos have shown reluctance in pursuing. In addition, the people still cling to their ancient value, family interests over individual gain. Personal economic pursuit, individual initiative, and aggressive behavior are discouraged in Papago society.

As is the case with many of the American Indian tribes, significant social and economic problems currently exist on the Papago reservation. Extremely high rates of unemployment, alcoholism, and social unrest are indicative of a troubled population. The process of economic infantilization which began in the early part of the century made the Papagos almost entirely dependent on the federal government for all human services. A lack of individual and tribal self-sufficiency and pride were fostered by the scores of government programs bolstered by huge Bureau of Indian Affairs (BIA) budgets. The chronic state of demoralization that had existed on the reservation has recently worsened due to a reduction in the BIA budget by the Reagan administration.

The tribe, which is totally dependent on federal aid, fears a return to the poverty which existed prior to the massive federal aid programs. The only note of optimism is that the Papagos are a hearty and resourceful people, both physically and emotionally adapted to rough times.

American Indian Health

The state of health of the American Indian prior to the arrival of whites in the New World is uncertain. Several researchers believe that the Native Americans were spared the epidemics which ravaged Europe in the Middle Ages, perhaps a result of the filtering of harmful microorganisms by the cold screen of the Arctic land bridge connecting the Americas to the Old World (5). Hrdlicka's findings that thousands of pre-Columbian American Indian bones were disease-free have been widely cited as evidence for the excellent health of these people prior to the arrival of Europeans (6). Undoubtedly the harsh environment of North America selected out only the hardiest individuals. With the arrival of the Europeans in the fifteenth century, the Indian population was ravaged by successive epidemics of rubella, influenza, pneumonia, and smallpox. Some researchers attribute the decimation of the Indian population to an increased racial vulnerability to certain infectious diseases (7).

In the early 1800s, U.S. military physicians working in the American Southwestern Territories made an effort to curb the spread of smallpox among the Indians. The devastating epidemics severely reduced the tribal populations to a fraction of their original numbers. The efforts of the military doctors resulted in a treaty in 1832 between the federal government and various Indian tribes which provided health care. These medical services were subsequently guaranteed by laws and treaties enacted by Congress and authorized by the U.S. Constitution. Responsibility for administering the medical care was assigned to the Public Health Service, initially part of the Bureau of Indian Affairs (BIA). At that time the BIA was a branch of the War Department. In 1849 the BIA was transferred to the Department of Interior; in 1955 it was again transferred to the Department of Health, Education, and Welfare. The successor to that department, Health and Human Services, retains the BIA.

The Indian Health Service (IHS), still part of the Public Health Service, has grown steadily since its origin in 1832. By 1900 it employed 83 physicians; at its peak in 1978, 600 physicians were at its command. In addition, in 1978 there were a total of 51 hospitals, 99 health centers, and more than 300 health stations and satellite field clinics. Although these services have contracted greatly under President Reagan, the IHS remains a vibrant entity and still provides the vast majority of health care for American Indians.

Health Care on the Papago Reservation

Modern health care has been freely available to the Papago for less than 50 years. Despite the vastness of the reservation and the remoteness of many villages, almost everyone has access to the hospital facilities and has frequent contact with trained health care workers. Most of the routine medical care in the Papago villages is provided by trained natives and Anglo nurse practitioners, who travel throughout the reservation. They are responsible for providing on-going preventive and therapeutic services, especially to patients in remote areas or who are unable to travel. In addition, there are three satellite medical clinics located in strategic areas of the reservation, which are manned by Papago medics, trained at the University of Arizona Medical Center. Tribal members are also free to obtain outpatient health care at the 40-bed IHS Hospital in Sells, a fully equipped modern facility which employs eight full-time physicians. Most patients requiring hospitalization go to that hospital. Patients requiring surgery or more sophisticated services are transported to medical centers in Tucson or Phoenix.

In an emergency, all the villages are connected via two-way radio to the IHS Hospital in Sells and the satellite clinics. Community Health Representatives (CHR) are located in most of the villages and are responsible for making known the health care needs of the people during emergency and routine situations. An emergency patient is usually brought to a satellite clinic by the CHR and is either treated there, or triaged to the IHS Hospital in Sells, or if necessary transported by ambulance or helicopter to a larger medical center in Tucson or Phoenix.

The tribe also owns an experimental Mobile Health Unit which was jointly funded by the IHS and NASA in the 1970s. The unit is a totally self-contained clinic which can be driven to any part of the vast reservation to diagnose and treat an acutely ill patient when a physician is not immediately available. It is capable of transmitting to the physicians in Sells a televised picture of an ill patient along with the ECG, x-rays, and any sound that can be auscultated or percussed. Unfortunately the funds for the maintenance of the equipment have been significantly reduced and the Mobile Health Unit is currently functioning as an independent mobile clinic.

During the past twenty years, one of the world's most sophisticated computerized medical record systems has been installed at Sells to provide online and rapid access to a patient's medical record by workers in the field and the IHS facilities. The complete medical history of every Papago is contained in the computer and gives IHS health providers an up-to-date summary of a patient's clinic encounters and hospital admissions, complete with diagnoses and therapies. Furthermore, there is a record of all preventive services, such as immunizations and Pap smears and when the next service is due. The system was utilized by Dr. Lawrence Weed, M.D., and his associates to develop the problem-oriented medical record.

Traditional Papago Concepts of Health Care

Despite the highly organized system of modern health care which exists on the reservation, the practice of native medicine remains an important factor in the lives of the Papago Indians. Health is taken quite seriously by the Papagos. Whenever they have illness, called "mumkidog," they are likely to first approach a tribal medicine man, the "mahkai." The role of the "mahkai" is to diagnose the cause of illness. They are also known to perform other duties, such as forecasting the weather, foretelling the future, and predicting natural disasters (8). The "mahkai" has a very important position in Papago society and his skills are passed on from father to son. Ruth Underhill, an American anthropologist who lived among the Papagos for 20 years, once wrote: "Medicine men could also work magic and make rain. Sometimes medicine men had great contests to show which village had the most power. Rival medicine men would swallow sticks and eat coals—the one who could do the most was sure that his village would win" (9).

The Papagos describe their illness to the "mahkai" as being either a "pain" or a "sore." Its location, whether it is "deep" or "superficial," and its severity ("serious" or "not so serious") are also described. For example, common complaints are "not serious superficial belly pain" and "serious deep foot sore."

The Papagos believe that certain "Beings" such as animals, plants, and natural phenomena have supernatural powers (10). One way in which illness can occur is when a person disturbs the harmony of these powers. It is the role of the "mahkai" to determine the imbalance and name the disease according to which "Being" has been disturbed. Common diseases are "horned toad disease" and "whirlwind disease," each of which has a characteristic symptom complex (11). The "mahkai" will then send the patient to a native singer-healer, or "wusotdam." Through singing at the bedside of a sick patient, often for days, the "wusotdam" drives away the spirit of the "Being" that has been disturbed and has caused illness in the person. For a "wusotdam" to be capable of healing, it is necessary that he has familiarity with the involved "Being." Therefore, the more experienced singer-healer is more valuable in his power to heal. Experience can be attained either through direct encounters or through dreams in which the "Being" appears. The songs of the "wusotdam" usually contain rather abstract lyrics, often relating to their life experiences.

If illness has not been due to the disruption of a "Being's" harmony, a "mahkai" will recognize this and the patient will be referred to a herbalist, or "kullan maddam." The herbalist makes potions, which frequently induce vomiting. The vomitus is inspected to further aid in diagnosis. Alternatively, the herbalist will prescribe a special diet that eliminates certain foods or spices and this is thought to be curative.

Occasionally, the "mahkai" will diagnose an illness which requires the aid of a masseuse-healer, or "dagimundam." This person heals through the massage of various organs thought by the "mahkai" to be "out of their proper position" in the body. Broken bones and dislocated joints are healed in this fashion, often harming the patients and frustrating the IHS health care workers. If a "mahkai" is unable to determine the etiology of a patient's illness, it is considered to be a "White Man's disease" and the patient is referred to the IHS facilities. Certain diseases such as diabetes mellitus, cancer, and most infections are thought to be in this category.

Among many of the American Indian tribes, modern medicine has not had widespread acceptance. The Papagos are fortunate in that they do not have many of the conflicts that characterize the interface between traditional and modern medicine. Perhaps the relative ease with which the Papagos have accepted modern medicine is due to the compatibility of Papago and modern concepts of health care delivery. For example, the Papagos view surgeons and radiologists as diagnosticians, like the "mahkai." General practitioners and dentists are seen as healers, much the same way as the herbalists, singers, and masseuses, all of whom relieve suffering by touching the patient or dispensing medicine (12).

Unlike the usual practice in many ancient cultures of choosing either a native healer or a modern doctor, many Papagos seek the advice and cooperation of both traditional and modern health care providers. "Mahkai" often cooperate with the IHS doctors and "mahkai" are commonly seen in the hospital giving advice to patients and IHS workers. A free interchange exists between the new and the old in a unique way that enhances patient care.

Despite the ability of the two different health care systems to complement each other, the Papago concepts of health can occasionally clash with the tenets of modern medicine. Papagos place supreme importance in the determination of the cause of illness and thus great faith in the abilities of their diagnosticians, the "mahkai." The Papagos frequently become frustrated with the IHS doctors who are often unable to determine the etiologies of their diseases. Likewise, the IHS doctors experience great frustration with their Papago patients. Precise symptomatology and the ability to discern the temporal progression of illness, which are important tenets of modern medical diagnosis, are not within the Papago concepts of disease. This often accounts for the poor compliance with therapeutic regimens among the people. This is an especially serious problem with diseases of unknown etiology or without a known cure, such as diabetes mellitus and hypertension.

Contemporary American Indian Health

The overall state of health of the contemporary American Indian population is uniformly poor. Although Indian infant mortality between 1955 and 1978 declined from 61 to 18 infant deaths per 1000, it still remains higher than the overall U.S. infant death rate (13). Likewise, life expentancy among American Indians lags 6 years behind the rest of the American population. The age-adjusted death rate for the American Indian is 1.3 times the U.S. all-races rate. Overall mortality rates among Papagos as compared to the rest of the U.S. population (Table) in 1975 (14) clearly indicate that most of the mortality is related to low socioeconomic status and/or poor environmental conditions. However, certain diseases, such as diabetes mellitus, have an unusual propensity to afflict the American Indian population. The reason for this is not clear, although the problem is undergoing intensive study.

TABLE

Leading Causes of Death (1975): Papago Indians, All U.S. Indians, And All U.S. Population
(rates per 100,000)

Causes	Papago Indians	All Indians	All U.S.	Ratio Sell:U.S.
All causes	900.6	824.8	888.5	1.0
Accidents	160.8	170.5	48.4	3.4
Heart disease	93.8	147.4	455.8	.21
Malignancy	75.1	79.8	171.7	.44
Cirrhosis of liver	72.4	61.4	14.8	4.9
Influenza/pneumonia	32.2	36.1	26.1	1.2
Cerebrovascular disease	26.8	43.5	91.1	.30
Diabetes mellitus	24.1	23.8	16.5	1.4
Suicide	24.1	26.0	12.7	1.9
Homicide	21.4	26.5	10.0	2.1

Diabetes Mellitus

The Papagos, and their neighbors the Pimas, have an unusually great propensity to develop diabetes. Between 50% and 70% of all adult Papagos older than 35 years will develop the disease (15). It appears that diabetes is a new affliction for both these tribes. When Dr. Eliot Joslin in 1939 studied the Arizona Indian population, he concluded that diabetes was no more prevalent among them than among the rest of the American people (16). By 1967, these same tribes were shown to have several times the number of diabetes-related deaths than the overall U.S. population.

Diabetes among the Papagos, according to this author's experience, is almost entirely adult-onset or Type II and resistant to ketosis. There is a strong association with HLA antigen A2 and not with HLA antigens B8 or B15, which are usually associated with Type I or juvenile-onset diabetes (17). Studies have also shown that islet cell antibodies are rarely present (18). In most cases, patients are not insulin dependent but tight control with oral hypoglycemic agents is difficult to obtain.

Diabetes among the Papagos has a clear familial aggregation. Studies of the Pimas have shown the incidence of diabetes to be 9% in the offspring of 2 parents with the disease, as compared with 1.6% in offspring of healthy parents (19).

Many researchers believe that the prevalence of diabetes among the Papagos and Pimas is related to the almost ubiquitous obesity. Studies have clearly shown that the tribes with the highest rates of diabetes have the greatest amount of obesity (20). Research has yet to prove that obesity is an independent variable that can cause diabetes over an extended period of time. Nilsson's findings suggest instead that obesity is genetically linked to the diabetic trait. In his work, he was able to show that infants born to normal mothers and diabetic fathers have increased birthweights (21).

An interesting hypothesis has been generated in recent years to help explain this fascinating problem. Historically, the Papagos were subject to harsh living conditions and chronic shortages of food. Neel reasoned that the people evolved a specific genotype which made survival possible under alternating periods of abundance and famine (22). This gene would provide the body with the capability of hyperinsulinemia which would promote increased adipose tissue during periods of food surplus. Studies among normal healthy Pimas have shown that they have higher fasting and post-glucose load insulin levels than matched controls (23). When food became scarce, the Papagos survived on their fat stores. In the modern world, the Papagos have free access to abundant food supplies. It is possible that a once "thrifty" genotype has made them poorly adaptable to their current lifestyle.

Like all persons with diabetes, the Papagos suffer from the multiple vascular complications of this chronic disease. But the prevalence of the different complications varies significantly from other races. Renal disease and related deaths are 3–4 times more common among the Papagos and Pimas than among white diabetics. Cardiovascular complications which are very common among white diabetics are relatively rare among the Indians (24).

In addition, the Papagos are afflicted disproportionately with a multitude of other complications, including soft tissue infections and gangrene. Fetal loss and congenital malformations related to diabetes are surprisingly common (25).

The treatment of the diabetic Papago is a difficult problem. Since most patients make only limited attempts at weight loss, medication is almost always necessary. All of the major oral hypoglycemic agents are currently being prescribed and their success varies with the individual patients. Patients frequently fail to respond to the oral agents and then are placed on insulin. Combination therapy, oral agents and insulin, has been used successfully on the reservation. In general, patient compliance is poor and tight control of blood glucose is virtually impossible. Very few Papagos are motivated to monitor their blood glucose levels or even to check their morning urines. In a few motivated patients, tight control has been possible.

The reasons for the lack of patient compliance with treatment regimens are uncertain. It is the belief of the author that it is related to the Papago conception of illness. The traditional belief system emphasizes knowing the cause of illness and curative treatments. In the case of diabetes, the IHS doctors are unable to provide this information to their Papago patients. Despite a tremendous joint educational effort by the Papago and IHS leadership, compliance remains poor. It is the belief of the authors that patient health education should be more compatible with the Papago belief system. The IHS personnel need to work more closely with the tribe in developing a comprehensive approach in treating patients. More emphasis should be placed on the importance of diet and total family involvement. The current scientific approach in exploring the disease and its treatment should be deemphasized.

Conclusion

Solutions to the health care problems of the Papago people will be difficult to create. Most of their health problems have resulted from a significant disruption of their culture and once-adaptive way of life. Their diseases are multifactorial in origin. Diabetes, for example, appears to result from the interaction of a currently maladaptive gene to a new lifestyle. No doubt the increased emotional stress which the Papagos experience and the alterations in their diet are major contributors to disease. Hopefully the future will bring a greater balance between the traditional Papago way of life and modern America.

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Ultrastructural Study of the Faces of Diseases

MARCELINO G. REYES, M.D., AND KIMI TERAMURA, M.S.

Abstract

Using the electron microscope, we found pretty, bratty, serene, proud, and grumpy faces in a malignant neuroectodermal tumor of the brain, a muscle capillary in suspected myositis, an ovarian neoplasm, an obscure neuropathy of the sural nerve, and the cerebral cortex of suspected herpes zoster encephalitis. Our findings suggest that faces may be more common in neoplastic and nonneoplastic diseases than was previously thought. Moreover, we suspect that the pathologist who sees these faces may have a better prognosis than pathologists who do not.

Introduction. A chance finding of a pretty face in the electron-microscopic examination of a malignant brain tumor in a child led us to a systematic search for faces in other tissues.

Materials and Methods. Electron micrographs of neoplastic and non-neoplastic tissues constituted the study. Using a double-blind technique, we selected the electron micrographs with faces and independently noted our diagnosis. Next, we showed the faces to other pathologists in our department and to outside consultants and compared their diagnosis with ours.

Results. 1. Malignant neuroectodermal tumor in the right frontal lobe of a 13-year-old boy. A corner of one of the electron micrographs showed a face in a mitochondria (Fig. 1). Our diagnosis: a pretty face. Our consultants concurred with our diagnosis.

2. Muscle biopsy of a 43-year-old woman with suspected myositis. One of the capillaries showed a face in its lumen (Fig. 2). Our diagnosis: a bratty face. Some of our consultants thought the face resembled ET; while others thought they saw Charlie Brown when they looked at the face upside down.

3. Ovarian neoplasm in a 39-year-old woman showed a face that was surrounded by an elaborate cristae in a mitochondria (Fig. 3). Our diagnosis was a serene face resembling the Sun Goddess. An outside consultant saw a resemblance to Queen Victoria.

4. Sural nerve biopsy of a 40-year-old man with chronic neuropathy of unknown etiology. A myelinated nerve fiber above a Schwann cell showed a face (Fig. 4). Our diagnosis: a proud face of a little boy with a bow tie. Some of our consultants suggested Popeye. Others who turned the figure upside down saw a kid with a mouthful of cookies.

5. Cortex of temporal lobe of a 67-year-old woman with suspected herpes zoster encephalitis. A myelinated fiber showed a face with a long neck (Fig. 5). Our diagnosis: a grumpy face. Our consultants gave diagnoses of dog, giraffe or ostrich face, man with a long nose, and man with a moustache. Our final diagnosis: face, grumpy. We chose this over face, type not otherwise specified.

Comments. When pathologists use their microscopes, they look for bodies to help in diagnosis—Lewy bodies in Parkinson's disease; with the electron microscope, zebra bodies in Hurler's disease—to name a few. In contrast, the pathologist rarely looks for faces. Perhaps rightly so, because faces are unlikely to offer clues in diagnosis. However, when we see the joy of those who look at these faces, we cannot help but think that they—the faces—have a therapeutic value.

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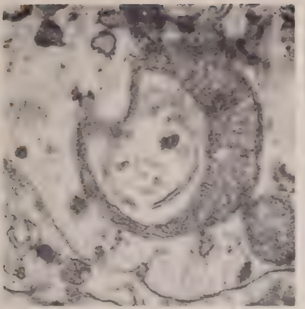

Fig. 1. Pretty face.

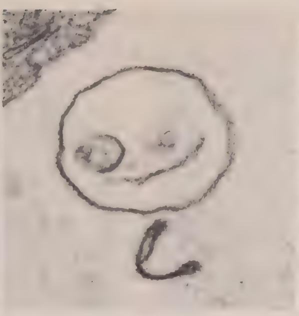

Fig. 2. Bratty face.

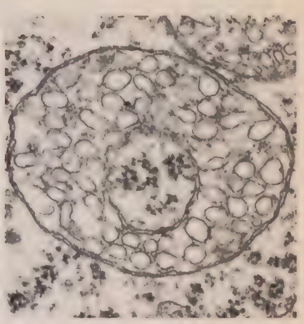

Fig. 3. Serene face.

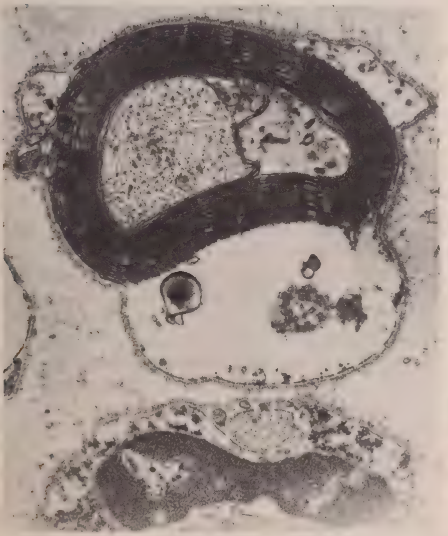

Fig. 4. Proud face.

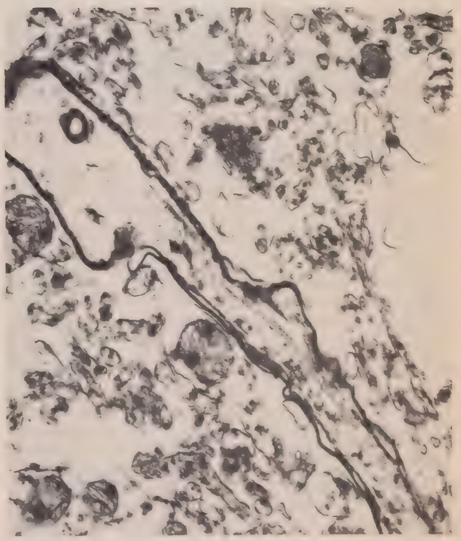

Fig. 5. Grumpy face.

Pathology Notes *William Thomas, Jr., M.D., Editor*

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Cholesterol Emboli Causing Acute Gangrenous Cholecystitis

WILLIAM THOMAS, JR., M.D., AND PHILIP ZARET, M.D.

Abstract

"He poureth out my gall upon the ground." Job 16:13. There are three major mechanisms for the etiology of abdominal hollow viscus pain: distention, inflammation, and ischemia. With regard to the gallbladder, the physician is most commonly accustomed to seeing pain from the first two mechanisms, generally because of gallstones. In recent years, ischemia has also been described as inducing cholecystitis, secondary to vasculitis. A case report and pathological findings demonstrate that cholesterol emboli to the vasculature of the gallbladder may cause acute gangrenous cholecystitis. We believe this to be the first reported instance of cholecystitis induced by cholesterol emboli.

Ischemia has recently been described as inducing cholecystitis secondary to vasculitis (1). The case reported here demonstrates, we believe for the first time, that cholesterol emboli to the vasculature of the gallbladder may cause acute gangrenous cholecystitis.

Case Report. A 76-year-old black woman was admitted to the hospital for chest pain and uncontrolled hypertension. She had a history of extensive atherosclerotic disease, including myocardial infarction four months prior to admission; left femoral popliteal bypass 4 years prior to admission; hypertension for 10 years; and several transient ischemic attacks in the few months prior to her admission. She also had a history of chronic renal failure but was not receiving regular dialysis. She was maintained as an outpatient on isorbide dimitrate (Isordil), Digoxin 125 mg, and potassium supplements.

On examination, she was somewhat sallow and in moderate distress, complaining chiefly of pressurelike chest pain. Vital signs were: pulse 80, afebrile, blood pressure 240/120, and respirations 17. The neck was supple with no audible bruits or thyromegaly. Lungs were clear to auscultation. The heart revealed a moderate S_1, S_2 with a grade 3/6 systolic ejection murmur heard over the apex. Initially, abdomen and extremities were unremarkable except for an old femoral popliteal scar.

Electrocardiograms showed ST depression. The creatine phosphokinase was found elevated soon after admission. There was a high MB fraction. The blood urea nitrogen was 43 gm/dl, creatinine 5.6 gm/dl, hemoglobin 9.5 gm/dl, and hematocrit 26.1%. Chest x-ray disclosed moderate cardiomegaly. Thirty-six hours after admission, the patient began to experience severe generalized abdominal pain. Examination of the abdomen revealed diffuse rigidity and absent bowel sounds. Pulses in all extremities were intact. Systolic blood pressure fell to the low 100s and the patient was rapidly prepared for surgery. The tentative diagnosis was ruptured abdominal aortic aneurysm.

At exploration, a distended, partially gangrenous gallbladder was found. The aorta and other abdominal structures were unremarkable. No stones were palpated in the gallbladder or cystic duct intraoperatively. The common bile duct was not distended.

Gross Description. The serosa of the gallbladder was gray-green. The viscus measured 9

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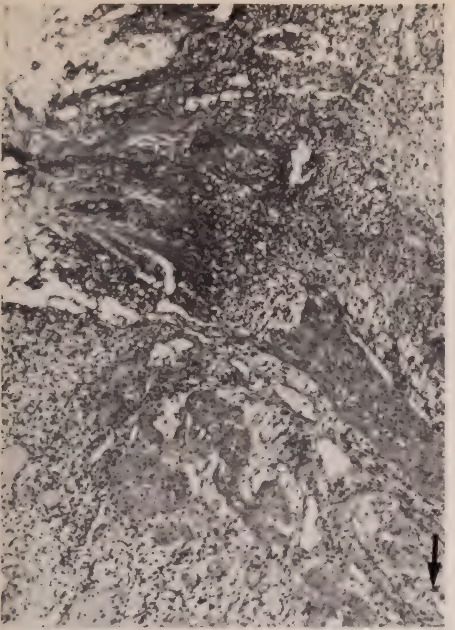

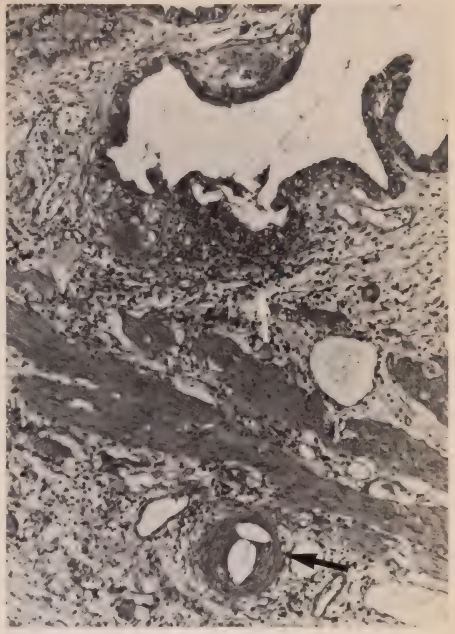

Fig. 1. Left Irregular cholesterol yeastlike cleft (black arrow) within organized thrombus that occludes medium-sized artery. Partially necrotic mucosa and inflamed muscle coat extend from above right to lower left (H&E ×20.5).

Fig. 2. Right Gallbladder displays focus of ulceration and acute inflammation (white arrow). Two cholesterol clefts (black arrow) occlude the lumen of a medium-sized artery in the muscle coat (H&E ×160).

cm in length, 3.5 cm through the largest diameter, and 1.5 cm near the neck. The gallbladder contained approximately 40 cc of green, viscid bile. There were no stones. The mucosa was focally discolored dark red and there was moderate edema. The wall measured 0.3 cm in thickness.

Microscopic Description. Histologically, there were multiple foci of acute necrosis of the mucosa and lamina propria. A rather dense neutrophilic infiltrate was in the necrotic area. The most striking change involved small and medium-sized arteries in the muscle coat. In general, the vessel coats were thickened and the lumen in many arteries contained acicular cholesterol clefts, often within organized thrombi. There was no inflammatory reaction in vessel walls. Small occluded branches of arteries were directed toward the base of the necrotic ulcers but did not directly abut the lesion (Figs. 1, 2).

Acalculous cholecystitis has been attributed to arteritis (2), post-traumatic and postoperative biliary stasis (3), hyperalimentation (4), thiazides (5, 6), and infectious agents (7). Blood supply to gallbladder may be a tenuous one, particularly in the elderly patient with atherosclerotic disease. In this age group, cholesterol emboli should be considered in the differential diagnosis of acute cholecystitis, both clinically and in surgical pathology.

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Duplex Scanning of the Carotid Arteries

DAVID COSSMAN, M.D., RICHARD TREIMAN, M.D., J. LOUIS COHEN, M.D., PHILLIP LEVIN, M.D., AND ROBERT FORAN, M.D.

The correlation between extracranial cerebrovascular disease and hemispheric transient ischemic attacks (TIA's) and strokes has been repeatedly documented (1, 2). The reliability of a bruit over the carotid bifurcation as a marker for significant stenosis, however, is uncertain, since patients with critical stenosis frequently have no bruit, while others with a bruit have little or no disease (3–5). Repeated arteriography is risky, expensive, and uncomfortable for patients with carotid bruits and is therefore an unacceptable method for following patients at risk for a stroke.

During the past fifteen years noninvasive techniques have been developed to detect hemodynamically significant stenosis at the carotid bifurcation. Oculoplethysmography (OPG), popularized by Kartchner and McRae (6), compares the pulse arrival time in the eyes by inserting pressure transducers attached to suction cups onto the cornea. An ocular pulse delay implies the presence of stenosis greater than 80% somewhere in the ipsilateral carotid-ophthalmic tree. The limitations of this study are its failure to localize lesions and its inability to detect bilateral stenoses and to subclassify arteries with stenosis of less than 80%. Since approximately half of TIA's and strokes are caused by ulcerative or nonulcerative lesions of less than 80% stenosis, OPG and other functional studies are inadequate means of assessing the symptomatic patient.

Other tests which noninvasively survey the extracranial carotid arteries are of passing historical interest. Carotid phonoangiography (CPA) is a high-resolution microphone which is nothing more than a sensitive stethoscope able to preserve noise on hard copy for future comparison. The supraorbital Doppler test is a simple means of detecting total or near total carotid occlusion by measuring reversal of blood flow in the supraorbital artery. Rich collateralization through the circle of Willis from either the contralateral carotid or the ipsilateral vertebral artery makes the overall accuracy of this test prohibitively low. Thermography has been generally discarded as a meaningful test for the noninvasive assessment of cerebrovascular disease.

High resolution ultrasonic B-mode imaging of the cervical carotid artery is capable of differentiating between normal and diseased bifurcations but is less sensitive in discriminating among various levels of disease (7). This shortcoming assumes major significance in selecting the asymptomatic patient for angiography and possible surgery. Duplex scanning combines ultrasonic B-mode imaging with real-time spectral analysis of a pulsed Doppler signal obtained from a small volume of blood within the sampled artery. Simultaneous imaging and Doppler signal analysis permit accurate classification of carotid bifurcation disease into broad but meaningful categories, including normal, mild to moderate stenosis, severe stenosis, and occlusion (8). Correlation with angiography is high, and under special circumstances some vascular surgeons have undertaken carotid endarterectomy without carotid arteriograms.

Spectral analysis of a small sample of blood within the common, internal or external carotid artery is based upon two basic hemodynamic principles. Fluid accelerates through a stenosis and, in general, recorded velocities of greater than 150 cm/sec in the internal carotid artery correlate with a severe stenosis. Graded stenoses will also result in turbulent blood flow distal to the area of stenosis. Spectral broadening, or disturbed blood flow, will result in a wide range of recorded velocities distal to a stenosis. The degree

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of broadening roughly correlates with percentage of stenosis.

Limitations of duplex scanning include:

- inability to interrogate the carotid siphon, intracranial vessels, or proximal common carotid artery.
- extreme operator dependency for accuracy.
- inability to define small ulcerations in symptomatic patients.

By combining duplex scanning with OPG, significant lesions proximal and distal to the area interrogated by the scan head may be suspected. Patients with carotid dissections resulting in stenosis or occlusion of the internal carotid artery, along with patients with fibromuscular hyperplasia, frequently have stenosis or occlusion remote from the carotid bifurcation. A normal duplex scan combined with an abnormal OPG will make the physician suspect that such a lesion may be present. Takaysu's arteritis or major arteriosclerotic plaques within the origins of the brachiocephalic vessels will also be missed with duplex scanning alone but will be suspected if the OPG is markedly abnormal.

Skilled technologists with adequate formal training and field experience are essential to minimize errors, particularly in the case of internal carotid artery occlusion. Erroneous identification of the external carotid artery in the presence of internal carotid artery occlusion has led to some significant false-negative studies.

Enthusiasts claim they are able to detect small ulcerations and describe plaque morphology using the duplex scanner, but in general only degrees of stenosis or the presence of occlusions are detected with reliability.

Comparisons of duplex scanning, digital subtraction angiography (DSA), and conventional arteriography reveal that DSA tends to underestimate and duplex scanning tends to overestimate the severity of disease when conventional arteriography is used as the "gold standard" (9). In less severe stenosis, however, there is reason to question the validity of arch and biplanar arteriography as the gold standard, since transverse and sagittal imaging of the carotid arteries will sometimes correlate more closely with surgical specimens than will the arteriogram.

Nevertheless, DSA, arteriography, and duplex scanning should be viewed as complementary rather than competing methodologies in evaluating the broad spectrum of carotid problems.

Duplex scanning is best utilized as a screening test for populations at risk of stroke, for patients with asymptomatic carotid bruits, and for evaluating post carotid endarterectomy patients for recurrent stenosis (10). For patients with hemispheric TIA's, formal arteriography is indicated.

Occasionally, when there is a relative contraindication to an arteriogram, a high-quality duplex scan will suffice for preoperative evaluation. DSA may be performed as an outpatient procedure, and in our practice it is a substitute for formal arteriography but is rarely used for screening of patients (such as preoperative evaluation of coronary artery bypass graft patients) or for evaluation of asymptomatic carotid bruits.

As improvements are made in the technology, it is hoped that duplex scanning will be used more and more to replace more invasive methods of carotid assessment.

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Student's Corner

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Gastric Carcinoma in the Young: Overview of the Literature

Mark G. Schwartz, M.D., and Nicholas A. Sgaglione, M.D.

Ninety-six percent of all malignant gastric neoplasms are adenocarcinomas, and the term "gastric carcinoma" generally refers to adenocarcinoma of the stomach. It is usually considered a disease of middle and late life, with a peak incidence between 50 and 70 years of age; the mean age at time of diagnosis is 55 years (1–4). However, gastric carcinoma is known to occur in younger individuals, including infants and children, although it is exceedingly rare in these youngest groups. It occurs in gradually increasing numbers with age. Since gastric carcinoma is rare in persons under 30 years of age, considerable interest attends each occurrence. This paper reviews the literature of gastric carcinoma in the young.

Age Incidence. Almost all of the investigators who have written on this subject have arbitrarily decided that 30 years of age is a convenient dividing time below which one considers cancer of the stomach as occurring in the young. The first three decades of life may be divided into two periods, ages 1 through 20 years, and ages 20 to 30 years. Occurrence in the first group is considered a clinical and pathologic curiosity. Cancer of any part of the alimentary tract in children is a very rare occurrence, accounting for no more than 5% of all pediatric neoplasms. The majority of malignant neoplasms of the stomach in children are lymphomas or soft-tissue sarcomas, with less than 6% identified as carcinomas (5). However, in 1877 Cullingsworth in the *British Medical Journal* described carcinoma of the stomach in a ten-day-old infant; this is one of the earliest authenticated reports (6).

Most cases of gastric carcinoma in the young occur in individuals between 20 and 30 years of age. These individuals, although still a small fraction of the total number of cases of gastric carcinoma, constitute a fairly constant percentage and show fairly uniform symptoms. The overall incidence of gastric carcinoma varies from country to country, Japan having the highest incidence and the United States one of the lowest. On the other hand, a similar occurrence rate is reported worldwide for gastric carcinoma in patients less than 30 years old. In general, the reported incidence of this disease in patients in the first three decades of life varies from 1% to 3% of the total cases of gastric carcinoma (1). Although this incidence is not high, it is clinically significant and one to be dealt with seriously.

The occurrence of carcinoma of the stomach in young people, although rare, has been known for many years. Golob, in 1923, reviewed the studies of earlier investigators and reported that 1% to 2% of gastric carcinomas occurred in patients under 30 years of age (7). Subsequent studies by Phillips (8), McNeer (9), Block (10), Bellegie (11) all reported that approximately 1% of gastric carcinomas occurred in patients less than 30 years of age.

More recently, in 1979, Bedikian published a paper dealing with 1,192 cases of gastric carcinoma seen at M.D. Anderson Hospital and noted 1.3% occurred in patients less than 30 years old (1). Two Japanese studies, by Furusawa in 1972 and Matsusaka in 1976, report an occurrence of 2.4% and 1.8% respectively in this age group, figures consistent with studies done in the United States (12, 13). Matsusaka states that the inci-

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dence of patients under the age of 20 is about 1/20 of that in the 20–30 year age group.

Sex Ratio. The sex ratio of gastric carcinoma shows a remarkably similar pattern in all countries from which data is available. The incidence is at least twice as high in males as in females, except in patients under 30 years of age. Studies by McNeer (10), Bellegie (8), and Matsusaka (13) all revealed that both sexes were equally involved under 30 years, as opposed to the male predominance (2–3:1) they observed in the older age groups. A female predominance of 2.5:1 in those cases under 30 years old was reported in studies by both Bloss (14) and Tamura (15), with an increase in the proportion of men with gastric carcinoma observed as the age of initial diagnosis increased. The explanation for this sexual predilection is not known. It is unlikely to be due to an age-sex differential in diagnostic accuracy or case fatality, as data from several large cancer registries show similar trends.

Etiology. Although environmental and dietary factors have been investigated in adults with gastric carcinoma, no specific etiologic agents have been clearly identified. Smoked and fried foods, as well as nitrates/nitrites, have been suspected as possible carcinogens, but a causal relationship still remains to be proven. The relationship of sex to total caloric consumption would fit the observed sex ratio pattern of gastric carcinoma after allowing for an appropriate latent period (16). The male/female ratio of total food intake is about 1, up to the age of puberty, at which time the ratio starts to increase, so that by late adolescence males are consuming 50%–65% more than females. This goes along with the hypothesis that a food-borne carcinogen is a necessary condition for carcinoma of the stomach to occur.

Diagnosis. Because of the rarity of gastric carcinoma in the young, the index of suspicion is typically low when the patient is 30 years or younger. It is often misdiagnosed as benign gastric ulcer, resulting in significant delay in treatment. This pitfall in diagnosis has been pointed out by many investigators (7, 8, 17–19). For years it was believed that benign gastric ulcers often underwent malignant degeneration. However, this theory has been abandoned, and it is generally accepted that a malignant gastric lesion is malignant from its beginning (20).

McNeer (10) cites age as the greatest stumbling block in establishing an early diagnosis, for the young patient with gastric carcinoma presents a clinical picture closely parallel to that of older patients. He points out in a review of 501 cases that the roentgenologic evidence of carcinoma was very often ignored or not considered seriously because of the age of the patient. In the face of obvious filling defects, a diagnosis of benign gastric ulcer was made time and time again. On many occasions the roentgen reports essentially stated that while the defects resembled cancer, the subject was too young to have the disease. As a result cases were treated by various forms of medical therapy, often for many months before surgical intervention was finally undertaken.

Block (9) reviewed all gastric lesions in individuals below the age of 31 years seen at the University of Michigan Hospital over a thirty-year period. He determined that although gastric lesions in youth are rare, when one does occur, there is a 30% probability of it being a carcinoma. Thus, the usual clinical dictum that a gastric lesion in a patient below the age of 30 years is probably benign is not necessarily true. He also found, as did McNeer (10), a tendency on the part of the physician not to diagnose cancer; benign gastric ulcer was nearly uniformly considered a more likely diagnosis in view of the patient's age. Once again, this led to delay in definitive surgical treatment. The average time for diagnosis after onset of symptoms in Block's study was 11.5 months, significantly longer than for the older patients.

The reluctance to consider the diagnosis of gastric carcinoma in early adult life is illustrated well in a study by Thomas (21), who looked at the delay between the onset of symptoms and eventual diagnosis. The young patients in his study with gastric carcinoma had persistent symptoms for an average period of 5 months before attending the hospital, which coincides with the delay recorded at that hospital in older patients. Nevertheless, after admission to the hospital an average interval of 3 months elapsed before the diagnosis was confirmed in the young group, whereas the diagnosis was reached within 2 weeks in the group of older patients. The recent studies by Matsusaka (13), Bedikian (1), and Bloss (14) cite a similar pattern in delay of diagnosis in the young group as compared to the older group. Although early complaints were nonspecific and sometimes indistinguishable from peptic ulcer disease, there was the tendency to overlook the possibility of a malignant tumor of the stomach, even when results of diagnostic studies were suggestive.

Upper gastrointestinal tract endoscopy is currently the best diagnostic aid, and it is recommended for use in evaluation of all young adults with gastric ulcers or persistent gastric symptoms. Complete prompt regression of clinical symptoms associated with total radiologic and endoscopic evidence of healing of a gastric ulcer can be construed as strong assurance of a benign lesion. Repeated followup is indicated until all of these conditions are met. Under medical therapy, significant healing of a benign ulcer should occur within 6 weeks. The great majority of malignant ulcers fail to heal promptly and completely, and laparotomy is then firmly indicated. Levine (22) reports that a standard upper gastrointestinal roentgenographic series often reveals an ulcerating lesion, but that the correct diagnosis of carcinoma may be missed in over half of these cases. Even in 1983, he attributes this to the radiologist's unwillingness to consider the possibility of gastric carcinoma in young individuals despite radiographic features favoring malignancy.

In equivocal cases, all known diagnostic aids should be used. Gastric cytology has been quite helpful in experienced hands. Determination of gastric acidity offers little help in the average case; however, an organic lesion in the presence of anacidity should always be viewed with alarm. It is estimated that the accuracy in diagnosing carcinoma of the stomach can reach as high as 98%, if upper gastrointestinal tract roentgenograms, gastroscopy, and gastric cytology are combined, and if the age of the patient is not allowed to be a deterrent (14).

Most studies are in agreement that the symptoms of gastric carcinoma in younger patients show few, if any, differences as compared to gastric carcinoma in older patients (2, 7, 10, 12–14, 19). Nevertheless, young patients had their symptoms longer before the diagnosis was established. The majority of patients had epigastric pain and postprandial discomfort, associated with loss of appetite, nausea, vomiting, weight loss, and early satiety. Less frequently, symptoms of hematemesis, melena, weakness, and dysphagia were described. Pain in young patients is often thought to be secondary to peptic ulcer disease, occasionally being relieved by antacids. Unfortunately, the symptoms of peptic ulcer are often indistinguishable from those of gastric cancer.

Physical examination is generally nonspecific, but some patients may have epigastric tenderness or a palpable upper abdominal mass, which in the majority of cases reflects the advanced state of the malignant process. However, a large growth with metastases may exist without being palpable. Thus, when upper gastrointestinal symptoms persist over a relatively long period of time, regardless of the patient's age, one must take advantage of all available procedures in order to make a definitive diagnosis.

Pathologic Findings. The location of the lesion in gastric carcinoma may be deceiving. In studies by Richardson (23), Tamura (15), Stock (4), and Hansen (2), 80%–90% of malignant lesions were found in the distal stomach, regardless of the patient's age. Unfortunately, this is also the most frequent site for benign gastric ulcers, and hence the physician may be lulled into a false sense of security.

On the other hand, Bedikian (1) reported that carcinomas in the young tended to be infiltrative, diffusely involving the proximal portions of the stomach, while those in older patients were more often ulcerative and located in the distal stomach. Similarly, Matsusaka (13) found that the tumors in the younger group occurred throughout the stomach and were more likely to show a scirrhous pattern and less likely to show a polypoid pattern when compared to older patients. He noted the malignancies in the younger patients to be larger and more advanced than those in the older group. Matsusaka further described a striking difference between these two age groups with respect to mucosal metaplasia. In the young group the gastric mucosa surrounding the carcinoma was almost the ordinary mucosa without any metaplastic changes, whereas in the older group the mucosa had marked metaplastic changes in almost all of the cases.

The number of cases of gastric carcinoma in the pediatric age group is too small to permit meaningful conclusions concerning anatomical configuration, usual locations, and histology.

Treatment and Prognosis. Prior to 1941, the diagnosis of gastric carcinoma in a young adult was widely believed to carry a much worse prognosis than in older patients. McNeer (10) presented the first significant rebuttal to this premise. He concluded that gastric carcinoma in young adults was strikingly comparable to its counterpart in the older age group in regard to resectability and prognosis. Despite the significantly longer delay in diagnosing gastric carcinoma in the young, the present overall 5-year survival rate is between 7% and 12%, regardless of age (20). Theoretically, if the time from onset of symptoms to diagnosis were equal in both age groups, then young patients with gastric carcinoma should have a greater 5-year survival rate than older patients. Many studies (1, 2, 8, 9, 13–15) substantiate this outlook regarding prognosis.

Surgical excision offers the best chance for cure or early palliation. The most common resection is subtotal gastrectomy, but procedures vary. The large number of young patients undergoing palliative surgery as opposed to curative resection again reflects the delay before surgical consultation is sought. Other forms of therapy include chemotherapy and radiation.

Routine screening has been used successfully in Japan, where a 92.5% 5-year survival rate was attained with gastric carcinomas limited to the mucosa and submucosa (early gastric carcinoma) (14). The proportion of patients diagnosed as having early gastric cancer increased from 5.7% in 1961 to 34% in 1969, reflecting public awareness and meticulous preoperative radiologic and gastroscopic examination of patients at high risk of having gastric cancer. This experience indicates that the prognosis is maintained in respect to patients (especially those under 30 years old) who present with symptoms suggestive of gastric carcinoma. Unfortunately, the decreasing incidence of gastric carcinoma in the United States and the relative rarity of this disease in the young limits the cost-effectiveness of routine screening in this country.

Summary. The incidence of gastric carcinoma in persons under 30 years of age is limited but significant. An inordinate delay in diagnosis is common, and is attributed to a low index of suspicion because of age and frequent misdiagnosis as peptic ulcer. No demonstratable reason indicates that the expectancy of cure for young people with gastric carcinoma should be any less than that for older patients so afflicted. In fact, earlier surgical exploration of gastric lesions in young adults is the key to improving the outlook. The hope for cure rests with the clinician who will send the patient with the discernable gastric lesion to the surgeon without delay. Long-term cures in young people with gastric carcinoma have been reported (23), and with greater awareness that gastric carcinoma occurs in young people, earlier detection and surgical resection will follow.

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Clinical and Pathologic Dilemmas in Tolosa-Hunt Syndrome: A Case Report

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Case Report. A 70-year-old white woman was admitted to the hospital for temporal artery biopsy. The patient had a right eye ptosis for one year and recent onset of right-sided facial paresthesia. There was a history of head trauma one year ago without loss of consciousness. After the head trauma the patient noticed diplopia. The patient was evaluated by an ophthalmologist and neurologist who found right 6th nerve palsy, mild right-sided ptosis, and right pupil ½ mm smaller than the left. Pupils were equally reactive to light and accommodation.

Over the course of the next several months, the patient's ptosis worsened. Competitive nerve stimulation tests were normal. An initially equivocal tensilon test was repeated and was normal. Right supraorbital pain developed but there was no report of retroorbital pain. Erythrocyte sedimentation rate was 60 mm/hour. A tentative diagnosis of temporal arteritis was made. The patient was placed on 15 mg prednisone per day. Right-sided "burning" and "throbbing" headaches which the patient had been experiencing intermittently for one year were ameliorated on prednisone; however, no improvement in ocular findings occurred. A vague 10-year history of an arthritic condition affecting the neck, hips, and knees was elicited. The patient was also being treated for dry eyes with artificial tears. Schirmer's test was not performed on this admission.

Hospitalization two weeks prior to this admission included testing by diagnostic computerized tomographic scan, bone scan, arteriogram and venogram of the head. On the basis of the test results, nasopharyngeal carcinoma or other anatomical lesions were considered unlikely. At that time, blood cell count, urinalysis, and stool guaiac were unremarkable and the patient was discharged.

On this hospital admission, the patient had almost complete ptosis on the right side without proptosis. Visual acuity was intact bilaterally. Extraocular movement was intact on the left but the patient had complete right-sided ophthalmoplegia. Marked right supraorbital tenderness was noted on palpation. The patient exhibited right-sided facial paresthesia in the V_1 distribution. The right pupil was sluggishly reactive to light. The conjunctiva and sclera were not injected. Fundoscopic examination was unremarkable.

By history, the patient had hypertension and Type II diabetes mellitus. Plasma glucose was 233 mg/dl. Other blood tests were normal. Blood cell count showed slightly elevated white cells with a left shift (13 bands). The remainder of the differential cell count was normal. Platelet count was increased with 1^+ toxic granulation. Urinalysis was within normal limits. Erythrocyte sedimentation rate ranged between 15–25 mm/hour while on 15–20 mg prednisone/day.

Differential Diagnosis. Ophthalmoplegia, or paralysis of the extraocular muscles, may be due to pathophysiologically unrelated disorders. These include vascular inflammatory processes, cranial nerve disease, or degenerative or inflammatory processes of the extraocular muscles themselves. The differential diagnosis of ophthalmoplegia includes temporal arteritis, aneurysm of the internal carotid artery, carotid-cavernous fistula, gummatous periostitis surrounding the orbital fissure, meningovascular syphilis with oculomotor palsy (1), trauma, neo-

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plasm (1), and ophthalmoplegic migraine (2). The absence of a radiologically demonstrable lesion in this patient narrows the differential diagnosis.

Barricks et al (3) noted that systemic processes such as giant cell arteritis (GCA) may be accompanied by ophthalmoplegia. Headaches having a "boring" quality with occasional paroxysmal exacerbations are commonly manifested in GCA. Tenderness over the temporal artery, in approximately 55% of reported cases of GCA (4), is the reason the terms "GCA" and "temporal arteritis" are frequently interchanged. Vertebral and ophthalmic arteries may also show granulomatous changes. Ischemic necrosis of the extraocular muscles secondary to cranial arteritis is the probable cause of ophthalmoplegia encountered in GCA. Diplopia and ophthalmoplegia are frequent manifestations. In one series, 5 of 14 patients demonstrated ophthalmoplegia with ptosis. Oculomotor signs and symptoms responded to corticosteroids (5). Severe visual loss occurs in 36% of untreated cases and may be accompanied by insignificant fundoscopic findings (6).

Periarteritis nodosa is a possible etiology of ophthalmoplegia. This disease most frequently affects young adults. It may manifest as blindness, diplopia, 7th and 10th nerve palsies, vertigo, and hemiplegia. Delirium and coma may ensue in more severe cases (2).

Bilateral ophthalmoplegia may be due to localized myositis. Signs of inflammation occur commonly within the orbit. Exophthalmos, edema of the eyelids, chemosis, and conjunctival injection may be seen. The pathology does not necessarily follow nerve distributions, thereby ruling out a primary neuritis.

Tolosa-Hunt syndrome, described in 1954 by Tolosa, is an infrequently diagnosed cause of painful ophthalmoplegia. Tolosa's original autopsied case in 1954 showed a carotid artery "wrapped in granulomatous tissue which did not obstruct the lumen of the sinus" (7). The process also involved the cranial nerves.

Histopathologic study of the region revealed a nonspecific inflammatory process in which the carotid artery enters the cranial cavity by passing through the wall of the cavernous sinus. The walls and septa of the sinus were infiltrated with lymphocytes and plasma cells. No polymorphonuclear cells were found. Fibroblastic proliferation and granulomatous lesions impinging upon the regional cranial nerves were seen. Neither the myelin sheath nor the perineurium was involved. The dura surrounding the nerves was edematous with inflammatory exudate. Palsy was probably due to pressure on the involved cranial nerves which were encased in tight connective tissue.

Hunt and his associates elaborated on the clinical findings of Tolosa's syndrome. In 1961, these investigators described the rapid onset of unilateral ophthalmoplegia accompanied by retroorbital pain. They defined the process as superior orbital fissure syndrome involving cranial nerves 3–6. Patients with optic nerve pathology had probable involvement of the orbital apex.

Levy et al (8) in 1973 reported a case with autopsy findings similar to those of Tolosa. X-ray changes were seen on angiography and venography. Orbital venography showed obstruction at the superior orbital fissure or in the cavernous sinus. Recanalization of the superior ophthalmic vein was shown after therapy with steroids. Carotid angiography demonstrated a smooth narrowing of the intracavernous segment of the internal carotid artery. This was presumed to be due to extrinsic pressure of granulation tissue within the sinus.

Hunt in his 1961 study (2) outlines valuable clinical criteria for the diagnosis of the Tolosa-Hunt syndrome. First, pain may precede ophthalmoplegia by several days, or may appear some time later. The pain is characteristically continuous, retroorbital, with a "gnawing" or "boring" quality. Second, neurological involvement may include the 4th, the 6th, and the first division of the 5th cranial nerve in addition to the 3rd nerve. Periarterial sympathetic fibers and the optic nerve may also be involved. Third, duration of symptoms may be for days or weeks. Fourth, spontaneous remission may occur, sometimes accompanied by residual neurological deficits. Fifth, recurrent attacks may occur at intervals of months or years. Sixth, angiographic and surgical exploration demonstrate no extracavernous involvement.

The clinical guidelines used to diagnose Tolosa-Hunt syndrome are valuable when histopathological confirmation cannot be obtained. Autopsy, however, is the only unequivocal method of making the diagnosis. Wilson (9) has cited cases where similar retroorbital pain has been linked to tuberculosis, aneurysm, neuroblastoma, and fibrochondroma. Haymaker and Kullenback (10) have proposed rheumatic disorders, periorbital periostitis, and vitamin deficiencies as possible etiologies of spontaneously occurring extraocular palsies. Although not included in Hunt's original set of seven criteria, improvement with steroid treatment is also used as a diagnostic test for Tolosa-Hunt syndrome. Smith and Taxdal (11) noted that "the administration of large doses of systemic steroids for 18 hours produces a dramatic response in painful ophthalmoplegia." Fowler et al (12), however, pointed out that painful ophthalmoplegia due to parasellar neoplasms also improved with steroid treatment.

No set of clinical criteria is pathognomonic of Tolosa-Hunt syndrome. Dramatic improvement of headache and cranial nerve weakness, while suggestive, is not specific for the syndrome. It remains a diagnosis of exclusion—"a distinct clinical entity, of unknown cause, which may be simulated by a variety of other diseases" (2).

Discussion. Definitive diagnosis in this case remains elusive. The patient demonstrates right 3rd, 4th, and 6th cranial nerve palsies. Cranial nerve 5 in the V_1 distribution is also involved. This is compatible with the superior orbital fissure syndrome cited by Hunt (2). Sluggish response to direct light with an intact consensual reflex on the right suggests right optic nerve pathology. Hunt localizes this pathology to the orbital apex.

Supporting the diagnosis of Tolosa-Hunt syndrome is the observation of irregularities in the right cavernous sinus on venogram. This venogram interpretation, however, is controversial and not conclusive radiological evidence for cavernous sinus involvement. The duration and progression of symptoms in the patient, and the alleviation of throbbing right unilateral headaches with use of prednisone is consistent with, but not specific for, Tolosa-Hunt syndrome. Absence of retroorbital pain speaks against a diagnosis of Tolosa-Hunt. Classical retroorbital pain may be masked or absent, however, due to the patient's prior treatment with steroids.

Differential diagnosis of the patient's ophthalmoplegia includes some relatively common and uncommon causes. Myasthenia gravis was ruled out on the basis of a negative tensilon test. Periarteritis nodosa was considered unlikely because of the age of the patient. Unilateral ophthalmoplegia is not consistent with myositis. Giant-cell arteritis, or temporal arteritis, can cause headaches with ophthalmoplegia and ptosis (6), and cannot be ruled out as an etiology of the patient's signs and symptoms.

To establish a diagnosis of Tolosa-Hunt syndrome it was necessary to rule out temporal arteritis. Temporal artery biopsy is essential to diagnose temporal arteritis. Biopsy documentation of granulomatous inflammation with fragmented internal elastic lamina establishes a diagnosis of temporal arteritis and constitutes an indication for a trial of high-dose steroids (5).

Biopsy, in this patient, was negative for granulomatous changes. This finding, however, does not rule out temporal arteritis. Focal granulomatous changes may be missed on the biopsy specimen. Biopsy is, therefore, a specific but not a sensitive diagnostic tool. A trial of high-dose steroids is frequently given in the absence of biopsy-proven arteritis. Diagnosis is made retrospectively based on clinical improvement with steroid use.

Although the result of temporal artery biopsy does not alter treatment, biopsy is common in the work-up of patients presenting with unilateral headaches and ocular findings. Albert et al (13) points out the procedure has no morbidity and provides occasional diagnostic information. It also provides tissue for pathological and immunological testing. Transmission electron microscopy has shown ultrastructural degenerative changes in the vessel muscular media. Understanding and ultimately controlling the disease will presumably be facilitated by information gained on tissue biopsy.

Steroids are the treatment of choice for both temporal arteritis and Tolosa-Hunt syndrome. The prognostic significance of making a diagnosis of Tolosa-Hunt syndrome, however, is not clear. Even with treatment, the disease course is unpredictable. No evidence exists for spontaneous remissions, and relapses may occur at intervals of months or years. The major morbidity is persistent cranial nerve pareses and there is no proof that residual deficits are lessened by corticosteroids (1). Similar to temporal arteritis, systemic neurological disease does not occur in Tolosa-Hunt syndrome. In this respect, the prognosis is good.

The final diagnosis of the patient's headache, ptosis, and ophthalmoplegia remains enigmatic. The constellation of cranial nerve findings points to Tolosa-Hunt syndrome. The quality of the unilateral headaches in the absence of retroorbital pain is more consistent with temporal artery pathology. A trial of high-dose steroids is indicated for both diseases. Progressive levator palpebrae superioris weakness in the patient may be due to inadequate steroid doses. Smith and Taxdal (11) recommend 60–80 mg prednisone/day for treatment of Tolosa-Hunt syndrome.

In summary, if higher doses of steroids do not result in clinical improvement, further study of this patient must be conducted to establish a diagnosis and to guide treatment. The value of temporal artery biopsy is equivocal since a positive or negative result does not alter treatment. A positive finding, however, would make a more insidious and serious lesion a less likely cause of the clinical findings. If treatment fails, it is imperative to rule out an occult neoplasm, primary or metastatic, in the area of the cavernous sinus. This demands more extensive radiographic study with a reassessment of the differential diagnoses.

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Student's Corner

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Late Dacron Graft Failure: Two Cases

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Abstract

The incidence of failure of knitted Dacron prostheses is thought to be significantly greater than previously reported in the literature. Two cases of late aneurysmal dilatation with interstitial hemorrhage are reported with a discussion of possible etiology of graft failure. The literature reports structural weakness in the host vessel resulting in false aneurysm and dilatation and nondistensibility of the prosthesis are major contributing factors. It is imperative that this complication of arterial grafting be recognized and critically evaluated for the causative factors of graft failure.

A variety of synthetic materials have been employed during the evolution of vascular prostheses. In the last two decades, Dacron prostheses have been proven to be the most reliable for arterial replacement. Despite many anecdotes of Dacron graft failure, documentation of this complication has been sparse in the surgical literature; only 148 failures have been reported in the past (1).

Complications associated with the use of synthetic arterial prostheses include graft dilatation, interstitial bleeding, and fiber breakdown with resulting holes or tears which may lead to hemorrhage or false aneurysm formation. There have been reports of aneurysmal dilatation and interstitial bleeding with knitted and woven dacron prostheses observed at or shortly following implantation (2, 3, 5) and up to seven years after implantation (2–11). Knox reported aneurysm formation in a femoral artery dacron prosthesis 5½ years after insertion (4); Edwards reported rupture of a light-weight dacron aortic graft with fatal hemorrhage after ten years (12).

Fiber separation, fragmentation, holes and tears of the prosthesis wall with bleeding and false aneurysm formation have all been reported in the surgical literature (13). False aneurysm may occur early after the primary operation, and infection or poor surgical technique is often implicated; or it may appear several years later.

Numerous theories have been advanced to explain the etiology of false aneurysm formation, especially those citing the failure of suture material. However, despite the use of nonbiodegradable synthetic sutures (polyethylene and polypropylene), aneurysms continue to appear (13, 14). The extent and progression of artherosclerotic disease and weakness of the host artery are also well known factors (15, 16). Other factors implicated are excess mechanical stress in hypertension (15, 16), placement of graft near an active joint (15), shearing and vibratory strain (17, 18), and end-to-side anastomosis (13, 16). Infectious and noninfectious causes have also been implicated (18). This report addresses late failure of two dacron arterial prostheses.

Case 1. A 67-year-old man with diabetes mellitus, and atherosclerotic heart disease complicated by failure and angina was admitted for suprapubic pain and swelling of one week's duration. He had bilateral above knee amputations in 1978 and 1979, cross-femoral popliteal bypass graft, and a left iliac Gortex bypass graft. He underwent a suprapubic exploration; a large hematoma with semiclotted blood was removed. A translumbar aortogram showed a patient iliac-femoral bypass graft, and no evidence of a false aneurysm or any graft crossing the suprapubic area; a pseudoaneurysm of the femoral-popliteal bypass graft due to disruption at the right fem-

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oral artery was also demonstrated. The graft was ligated and resected from the common femoral artery. Patient did well and was discharged twenty days later.

Case 2. An 86-year-old white woman with a history of myocardial disease had progressive swelling and tenderness of the left groin for one year. She had an iliofemoral bypass in March 1977. A translumbar aortogram at the time of admission showed extravasation of dye from the iliofemoral dacron graft. Exploration of the left groin showed a complete disruption of the graft and left common femoral anastamosis with formation of a large hematoma of the left groin and suprapubic area. The hematoma was evacuated and the distal end of the dacron graft was anastamosed to the common femoral using a Gortex graft.

Discussion. The propensity of aneurysmal dilatation and rupture has plagued the evolution of arterial replacement grafts. Since Carrel (19) noted dilatation of human-to-dog grafts in 1912, similar complications of heterograft arterial replacement in a wide variety of experimental situations (3) have been reported.

After Voorhees introduced the first porous plastic arterial prosthesis in 1952 (3), Nylon (20), Orlon (22), and Ivalon (27) have been tried experimentally; long-term observation revealed frequent aneurysmal dilatation and rupture (21), and the use of these materials was considered hazardous and unjustified in humans.

Dacron, however, has had an enviable record as an arterial substitute. Of the estimated 15,000 aortic aneurysms and a larger number of aortoiliac and femoral reconstructions performed in the United States alone each year (3), dacron has been used in the vast majority of these patients with an incidence of pseudoaneurysm formation of 2% up to now (17).

Knox (4) reported aneurysmal dilatation in a femoral dacron prosthesis 5½ years after implantation. This was an early graft of woven taffeta, calendered, low-porosity variety and was inserted in 1955. Pathologic examination of the defective graft revealed a loss of weave conformity with fragmentation that resulted in diltation. Wesolowski (6) reported a similar generalized enlargement in a femoral graft. The material was knitted dacron and dilatation occurred three months after insertion. Cooke (3) reported three cases of generalized aneurysmal dilatation occurring in dacron aortic prostheses. All these were knitted dacron and dilatation was detected at two years, and seven and five months, respectively. May (23) reported multiple aneurysmal dilatation in Dacron velour grafts attributed to a basic defect in the graft. Orringer (9) in 1972 described aneurysmal dilatation of an axillofemoral dacron prosthesis, caused possibly by fabrication flaws, intraoperative damage, or mechanical fatigue. Orringer (2) in 1976 reported eleven additional cases of failure of ultralightweight knitted dacron prostheses. Four patients had spontaneous intraoperative interstitial bleeding and two patients had delayed interstitial hemorrhage associate with anticoagulation.

It has been stated that plastics and elastomes have an inherent tendency to age. Incomplete crystalization prevents them from reaching a state of thermodynamic balance so they tend to change their molecular order in one direction, that is, to age (24). However, excellent function of dacron graft has been reported up to 23 years after implantation.

Edwards showed experimentally that dacron loses 10% of its strength after 100 days in canine tissue (12). Harrison also reported an 11% loss of strength of arterial dacron grafts in dogs after two years (25). Edwards cites data showing that dacron absorbs 0.1% of its weight in H_2O. Such absorption could explain dacron's loss of strength, since tissue fluids are weak acids and could attack the dacron ultrastructure. Edwards predicted that dacron could last about twenty years under optimal circumstances.

Merrill (26) suggested that dacron fiber deterioration may be due to the action of H_2O and lipid molecules at the sites of defects in polymer chains. This could cause osmotic splitting of the polymer in a slow, evolving process, aggravated by mechanical stress. Dvorak (27) hypothesized enzymatic degradation of the mechanically damaged fiber crystalline lattice. In long-term clinically satisfactory studies, Dvorak saw fiber splitting and described filament breakage of various types occurring in arterial dacron grafts removed up to 12 years after implantation. Filament damage was ascribed to torsion due to yarn texturing, knitting and mechanical wear caused by repeated moderate bending (27).

Berger and Sauvage (1) reported that all recovered deteriorated graft had multiple defects varying in size from 2 mm to 28 mm. The earliest changes consisting of enlargement of graft interstices due to yarn filament breakage. These minute breakdowns eventually enlarged and led to the development of aneurysms ranging from a few mm to 5 cm in diameter.

Nunn (8) using ultrasonic measurements, revealed dilatation of several types of dacron aortic grafts following inplantation. The degree of dilatation was variable, ranging from zero to 84% (mean of 18%). Implantation time ranged from two weeks to 138 months. Nunn classified graft dilatations into 3 types: (a) increase in graft diameter and length due to flattening of crimps as the graft is pressurized; (b) increase in diameter and decrease in length due to rearrangement of the textile structure; and (c) increase in diameter and possible increase in length due to deformation of the basic graft material.

Kim (7), using static and dynamic testing, showed that initial dilatation is the result of yarn slippage, and late dilation possibly occurs from load elongation behavior of fibers with insufficient time for fibers to recover during the cardiac cycle.

Nondistensibility has also been implicated as a possible mechanism for prosthesis failure. An artery has a diameter change of about 10% with each pulse wave (28). Thus, the anastomosis of a rigid structure to a distensible one results in undue stress of the suture line and subsequent rupture (28).

In our cases, a disruption of the suture line and/or rupture of the graft resulted in formation of a false aneurysm 4 and 5½ years after implantation, respectively.

The precise mechanism of aneurysm formation, especially after rupture may be difficult to ascertain, but many reports have implicated weakness of the host arterial wall, with loss of holding power of the sutures as responsible in 70%–90% of cases (14, 17, 28). Gaylis (28) states that rupture with false aneurysm formation can arise in only three possible ways: a defect in fabric of prosthesis, breakage of sutures, or weakness of the host artery due to hypertension, diabetes, wound complications or endarterectomy (2). These factors result in abnormal sheer stress at the anastomosis leading to disruption of the arterial wall and eventually false aneurysm formation.

With respect to breakage of sutures, it was demonstrated that if silk was used in the original anastomosis and a pseudoaneurysm occurred, it was associated with fracture of the silk 78.5% of the time (14, 16). Thus, most vascular surgeons have discarded silk for use in arterial anastomoses.

It was subsequently found that even nonbiodegradable stress (polyethylene and polypropylene) resulted in a high incidence of pseudoaneurysm formation (14, 17). Hollier (17) recommends using braided dacron as the suture of choice for prevention of pseudoaneurysm formation. Thus, it became obvious that the limiting factor in pseudoaneurysm formation is the host vessel wall and that breakage of suture and prosthetic failure are contributing factors (17, 28).

Summary. In our cases, no measurements of tensile strength or electronmicroscopic examination of the removed prostheses were performed, nor were the graft materials returned to the manufacturer for examination. However, various host physiological factors, such as diabetes and atherosclerosis, could be implicated.

There has been insufficient documentation of the failure of dacron prostheses, what little has appeared in the literature has been evaluated from clinical and pathological points of view rather than an ultrastructural analysis as a cause of graft failure. Many variables must be considered in the analysis, including various polyethylene terephthalate (dacron) preparations, differences between graft batches and construction, variations in processing, surgical handling, host physiology, tissue response, and difference in tensile strength of graft material (1, 14, 17, 28).

Deterling (13) has urged that all graft failure be reported with details on material, construction, sutures used, and some critical evaluation of the causative factors. Kim and Wesolowski recommend the formation of a clinical vascular registry to record the behavior of prostheses after implantation so that outer diameters are recorded after implantation and prior to closure of the wound (7, 31). Nunn (8) suggests periodic postoperative ultrasound evaluation, since dacron grafts tend to dilate after implantation and may progress to graft failure and possible aneurysm formation, years after implantation. In this way a better, longer-lasting and safer vascular prosthesis may be developed.

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Index to Volume 51

Abnormal mucosal fold patterns in the duodenum, Seaman WB, 51(4):421–428.
Abortion on demand, Rovinsky JJ, 51(1):12–14.
Abramson A, Sperling R, Moshirpur J: Harlequin fetus in twins, 51(3):290–291.
Adenocarcinoma arising in Barrett esophagus: pathologic and radiologic features, Keen SJ, Dodd GD, Smith JL Jr, 51(4):442–540.
A dozen pediatric ultrasonic donuts, Teele RL, 51(4):528–534.
Agha FP, Whitehouse WM: Carcinoma of the esophagus: its varied radiologic features, 51(4):430–441.
A history of medical research at Mount Sinai Hospital Medical Center of Chicago, Westerman MP, Tymorek S, 51(2):150–156.
A hospital's response to the increasing incidence of child abuse and neglect in an inner-city population, Levy HB, Sheldon SH, 51(2):161–165.
Ahwah I: Late dacron graft failure: two cases, 5(6):728.
Amelar SE: *see* Lewis W.
An association of parotid carcinoma with Von Hippel-Landau syndrome, Nardi L, Constantini S, 51(3):298–299.
Anesthesiology at the turn of the century: where do we go from here? Greene NM, 51(5):595–599.
Anesthetic management of a patient with Osler-Weber-Rendu disease and chronic
Anterior pararenal-space infection from col and appendiceal perforation, McCort JJ, 51(4):482–490.
Anthracycline antibiotics as cellular disruptors: insights into anthracycline-induced cardiomyopathy, Lewis W, Amelar SE, Puszkin S, 51(3):246–253.
An unusual cause of tetany: surreptitious use of furosemide, Kaufmann H, Elliovich F, Yahr MD, 51(5):625–628.
Arterioportal fistula as cause of hypertension, Pang D, 51(5):644–646.
Aubry WM, Sparks JC, Braunstein GD: Parathyroid hormone measurements in hemodialysis patients as assessments of renal osteodystrophy, 51(2):132–137.
Aufses AH: *see* Salky B.
Autopsy, Geller SA, 51(1):77–81.
Autopsy, Rabbinic comment, 51(1):82–85.
Awards, *The Mount Sinai Journal,* 1983/84, 51(5):601.

Baratti MD: *see* Perec CJ.
Bauer JJ: *see* Keller RJ.
Begun MS: Triage of resources from institutions to departments, 51(1):104–105.
Begun MS: *see* Discussion, Triage of scarce resources.
Bell JA, Bluestein BM, Danta I, Wanner A, Effect of inhaled ipratropium bromide on tracheal mucociliary transport in bronchial asthma, 51(2):215–217.
Beneventano TC, Frager DD, Wolf EL: Widened retrorectal space: some radiographic-clinical considerations, 51(4):467–472.
Berger Z: *see* Pap A.
Berk RN: *see* Clements JL.
Bernardino ME: *see* Torres WE.
Berry CC: *see* Harell GS.
Bindman AB, Eichenfield LF, Geller SA: Diagnosis-related groups: physician and abstracter reliability and financial significance of errors, 51(3):237–245.
Bjelland JC: *see* Hunter TB.
Blanche C: *see* Lee ME.
Bleicher MA: *see* Pober JM.
Bradley B: *see* Harell GS.
Braunstein GD: *see* Aubry WM.
Breast cancer: risk factors and etiology, Rico M, 51(3):300–304.
Bree RL: *see* Schwab RE.
Burkhalter JF: *see* Waks AU.
Butler RN: Old age: right to privacy and patient's right to know, 51(1):86–88; *see* Discussion (End of life).

Cain DR: *see* Lee ME.
Carcinoma of the esophagus: its varied radiologic features, Agha FP, Whitehouse WM, 51(4):430–441.
Cedars-Sinai Medical Center: affiliates with *Journal,* 51(1): v; history and introduction, 51(2):123; articles from, 51(2):123–145; Editorial, 51(6):649.
Celener D: *see* Tiscornia OM.
Cesa M: *see* Reder RF.
Chalmers TC: Triage of resources from government to institutions, 51(1):101–103.
see Discussion, Triage of scarce resources.
Changes in free histamine in peripheral circulation following cockroach-antigen challenge in asthmatics, Chang JL, Ryo UY, Kang B, 51(2):197–202.
Chang JL, Ryo UY, Kang B: Changes in free histamine in peripheral circulation following cockroach-antigen challenge in asthmatics, 51(2):197–202.
Childs CC: *see* Field SP.
Cholesterol emboli causing acute gangrenous cholecystitis, Thomas W Jr, Zaret P, 51(6):716.
Clements JL, Hixson GL Jr, Berk RN, Dodds WJ, Goldstein H: Gastrointestinal carcinoid tumors: analysis of 104 cases, 51(4):351–359.
Clinical and pathologic dilemmas in Tolosa-Hunt syndrome: case report, Gallati MT, 51(6):724.
Clinical applications of gastrointestinal motility tests, Cohen LB, 51(5):620–624.
Cohen BM: *see* Martinez LA.
Cohen LB: Clinical applications of gastrointestinal motility tests, 51(5):620–624.
Comments (Gastrointestinal radiology: a festschrift for Richard H. Marshak, M.D.), Singleton EB, McCort JJ, 51(4):312.
Complementary effect of cholecystokinin-octapeptide and soy flour treatment in chronic pancreatitis, Pap A, Berger, Z, Varro V, 51(3):254–257; corrections, 51(5):646.

Constantini S: *see* Nardi L.

Continent illeostomy, Keller RJ, Khilnani MT, Bauer JJ, Gelernt IM, 51(4):473–478.

Continuous monitoring of mixed venous oxygen saturation in clinical practice, McMichan JC, 51(5):569–572.

Corbet A: *see* Harell GS.

Cornell A: *see* Gendal ES.

Cresta MA: *see* Tiscornia OM.

Danta I: *see* Bell JA.

Definition of death and dying, Kabakow B, 51(1):69–72; Rabbinic comment, Feldman DM, 51(1):73–76.

Dhar SK: *see* Magana L.

De Lehmann ES: *see* Tiscornia OM.

De Peusner ICW, Perec CJ, Tiscornia OM: H-QNB binding in submaxillary glands subsensitized by chronic alcohol feeding, 51(6):664.

Deppe G: *see* Gleicher N.

Diagnosis of extrinsic abscesses affecting small intestine, O'Riordan D, Herlinger H, 51(4):347–350.

Diagnosis of Meckel's diverticulum in adults, Ho CS, Shewchun J, Greenberg GR, 51(4):378–381.

Diagnosis of polar hypertrophy of kidney: case reports and review, Martinez LA, Francis DA, Schilling KJ, Cohen BM, 51(6):697.

Diagnosis-related groups: physician and abstractor reliability and financial significance of errors, Bindman AB, Eichenfield LF, Geller SA, 51(3):237–245.

Diagnostic approach to colon bleeding, Waye JD, 51(4):491–500.

Discussion, Medical ethics: adolescence to adulthood; Gribetz D, Feldman DM, Greifer I, Rosner F, Tendler MD, 50(1):65–68.

Discussion, Medical ethics: beginning of life; Gribetz D, Feldman DM, Gordon MA, Hirschhorn K, Krasna I, Kravitz L, Rovinsky JJ, Tendler MD, 51(1):37–41.

Discussion, Medical ethics: end of life: Gribetz D, Butler RN, Feldman DM, Geller SA, Gordon MA, Greifer I, Tendler MD, Trainin I, 51(1):92–100.

Discussion, Medical ethics: triage of scarce resources: Moderator: Gribetz D; Begun MS, Chalmers TC, Gelman MA, Greifer I, Tendler MD, 51(1):116–120.

Dodd GD: *see* Keen SJ.

Dodds WJ: *see* Clements JL.

Dose-related nephrotic syndrome in penicillamine-treated rheumatoid arthritis, Spiera H, 51(6):695–696.

Dreiling DA: *The Mount Sinai Journal:* Future, 51(1):v; Introduction to 3 new affiliates of the *Journal,* 51(2):121; Editorial, 51(6):649; *see* Greenstein RJ: Perec CJ: Tiscornia OM.

Dreyfuss JR, Janower ML: Single-contrast or double-contrast barium enema: a historical and philosophical perspective, 51(4):461–464.

Effect of DL-ethionine, cholecystokinin, and cerulein on pancreatic secretion and tissue composition in rats, Papp M, Varga G, Fodor I, Szabo D, Folly G, 51(6):680.

Effect of inhaled ipratropium bromide on tracheal mucociliary transport in bronchial asthma, Bell JA, Bluestein BM, Danta I, Wanner A, 51(2):215–217.

Effect of splenectomy on the growth of carcinogen-induced experimental bladder cancer in mice and rats, Ornellas EP, O'Brien A, Thomas W Jr, Lee RE, Moon RC, Westerman MP, 51(2):166–173.

Effects of antithymocyte serum on cardiac allograft survival in thymectomized-splenectomized rats, Racelis D, Martinelli GP, Schanzer H, 51(3):262–267.

Effects of cryopreservation on lymphocytes of homosexual men with generalized lymphadenopathy, Venkataraman M, Westerman MP, 51(2):174–179.

Effects of hydrocodone bitartrate on breathing pattern of patients with chronic obstructive pulmonary disease and restrictive lung disease, Sackner MA, 51(2):222–226.

Eichenfield LF: *see* Bindman AB.

Elastofibroma dorsi, Lee ME, Cain DR, Blanche C, 51(2):138–140.

Elliovich F: *see* Kaufmann H.

Ellrodt GD: *see* Murata GH.

Entrainment of microspheres within blood flowing through microarteries, Harell GS, Taylor M, Berry CC, Corbet A, Bradley B, 51(4):552–558.

Epstein M, Stern AJ: Postsurgical adult respiratory distress syndrome: case report, 51(3):305–310.

Esophagus and stomach after proximal gastric vagotomy, Smith HJ, Willeford G, Aueron FM, 51(4):417–420.

Evoked potentials in diagnosis, prognosis, and management of neurologic and neurosurgical patients, Moskowitz N, 51(5):640–643.

Evoked potentials in the operating room, Grundy BL, 51(5):585–591.

Feldman DM: Rabbinic comment on autopsy, 51(1):82–85; on definition of death and dying, 51(1):73–76; on rights of adolescents, 51(1):49–51; on teenage pregnancies and abortion, 51(1):20–24; *see* Discussion, Adolescence to Adulthood; Beginning of Life; End of life.

Feline genitourinary and systemic circulatory changes due to a vasopressin hormonogen, Greenstein RJ, Dreiling DA, 51(3):268–270.

Ferrucci JT Jr, Percutaneous drainage of abdominal abscesses and fluid collections, 51(4):547–551.

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Fodor I: *see* Papp M.

Folly G: *see* Papp M.

Frager DD: *see* Beneventano TC.

Francis DA: *see* Martinez LA.

Franken EA: *see* Lu CH.

Freeman R: In vitro fertilization and extra-uterine pregnancy ("test-tube" baby), 51(1):3–6.

Frick MP, Salomonowitz E, Gedgaudas E: The value of computed tomography in Crohn's disease, 51(4):368–371.

Fuster V: *see* Gorlin R.

Gallati MT: Clinical and pathologic dilemmas in Tolosa-Hunt syndrome: case report, 51(6):724.

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Gedgaudas E: *see* Frick MP.

Gedgaudas-McClees RK, McClees EC: Value of barium-swallow technique in evaluation of hypopharynx, 51(4):455–459.
Gelernt IM: *see* Keller RJ.
Geller SA: Autopsy, 51(1):77–81; *see* Bindman AB; *see* Discussion, Medical ethics: End of life.
Gellman MA: Rabbinic comment: Triage of resources to patients, 51(1):113–115; *see* Discussion, Medical ethics: Triage of scarce resources.
Gendal ES, Keller RJ, Sicular A, Waye JD, Cornell A: Radiology Notes: Case 2, 51(5):637–639.
Genetics, amniocentesis, and abortion, Hirschhorn K, 51(1):15–17.
Ginzberg E: Prospects in medical care: physicians, patients, practice, 51(3):258–261.
Gleicher N, Deppe G, Friberg J: Practice of tubal sterilization: review of a departmental practice pattern, 51(2):157–160.
Globus—Mount Sinai Journal Award, 51(5):601.
Goldstein H: *see* Clements JL.
Gordon L, Surgery Notes (ed), 51(6):718.
Gordon MA: Rabbinic comment: Old age: right to privacy and patient's right to know, 51(1)89–91; *see* Discussion, Beginning of Life; Discussion, End of life.
Gorlin R, Fuster V: Role of pharmacotherapy in secondary prevention of myocardial infarction and death, 51(3):229–236.
Graffiti Pharmacopeia, Marks SJ, 51(5):647.
Greenberg GR: *see* Ho CS.
Greene NM: Anesthesiology at the turn of the century: where do we go from here? 51(5):595–599.
Greenstein RJ, Dreiling DA: Feline genitourinary and systemic circulatory changes due to a vasopressin hormonogen, 51(3):268–270.
Greifer I: Infant with severe anomalies: should life-saving surgery be performed? 51(1):32–33; Transplantation surgery, 51(1):52–53; Triage of resources from departments to patients, 51(1):110–112; *see* Discussion, Adolescence to adulthood; Discussion, End of life; Discussion, Triage of scarce resources.
Gribetz D: *see* Discussion, Adolescence to adulthood; End of life; Triage of scarce resources.
Gribetz D, Tendler MD, guest eds, Medical ethics: the Jewish point of view, 51(1):1–120; Introduction, 51(1):1–2.
Griffin BM: *see* Silvay G.
Grundy BL: Evoked potentials in the operating room, 51(5):585–591.

Harell GS, Taylor M, Berry CC, Corbet A, Bradley B: Entrainment of microspheres within blood flowing microarteries, 51(4):552–558.
Harlequin fetus in twins, Abramson A, Sperling R, Moshirpur J, 51(3):290–291.
Hauser AD: *see* Ruchman RB.
Herlinger H: *see* O'Riordan D.
Hirschhorn K: Genetics, amniocentesis, and abortion, 51(1):15–17; Discussion, Beginning of Life, 51(1):37–41.
History and development of cardiovascular monitoring during anesthesia, Silvay G, Griffin BM, 51(5):560–568.
Hixson GL: *see* Clements JL.
Ho CS, Shewchun J, Greenberg GR: Diagnosis of Meckel's diverticulum in adults, 51(4):378–381.
Hodgson WJB: Splenic cystectomy and splenic preservation, 51(4)543–546.
Hoffman BH, Haskell AJ: Papago Indians: historical, social, and medical perspectives 51(6):707.
H-QNB binding in submaxillary glands subsensitized by chronic alcohol feeding, de Peusner ICW, Perec CJ, Tiscornia OM, 51(6):675.
Hunter TB, Bjelland JC: Life-threatening gastrointestinal complications of leukemia, 51(4):508–515.

Iatrogenic disease: an overview, Justiniani FR, 51(2):210–214.
Ileorectal and ileosigmoidal fistula in Crohn's disease: a clinical-radiologic correlation, Korelitz BI, 51(4):341–346.
Infant: right to privacy and patient's right to know, Krasna I, 51(1):25–28; Rabbinic comment, Tendler MD, 51(1):29–31.
Infant with severe anomalies: should life-saving surgery be performed? Greifer I, 51(1):32–33; Rabbinic comment, Kravitz L, 50(1):34–41.
Infective endocarditis in hypertrophic cardiomyopathy: case report and review of literature 1961–1982, Zimlichman R, Ovsyshcher IA, 51(5):614–619.
Interventional endoscopy in diseases of the biliary tree and pancreas, Siegel JH, 51(4):535–542.
Intraoperative esophageal electrocardiography, Kates RA, 51(5):573–577.
Introduction to Gastrointestinal radiology: a festschrift for Richard H. Marshak, M.D., Rabinowitz JG, 51(4):311.
Intubation infusion method: reliability in diagnosis of mechanical partial small-bowel obstruction, Maglinte DDT, Miller RE, 51(4):372–377.
In vitro fertilization and extrauterine pregnancy ("test–tube" baby), Freeman R, 51(1):3–6; Rabbinic comment, Tendler, MD, 51(1):7–11.
Iron absorption and utilization in maintenance hemodialysis patients: oral and intravenous routes, Magana L, Dhar SK, Smith EC, Martinez C, 51(2):180–183.

Jagirdar J: *see* Rimarenko S.
Janower ML: *see* Dreyfuss JR.
Justiniani FR: Iatrogenic disease: an overview, 51(2):210–214.

Kabakow B: Definition of death and dying, 51(1):69–72.
Kang B: *see* Chang JL.
Kantor I: *see* Levitan H.
Kaplan JA: Transesophageal echocardiography, 51(5):592–594.
Kates RA: Intraoperative esophageal electrocardiography, 51(5):573–577.
Katsoyannis G: *see* Salky B.
Katz SS: *see* Savitz MH.
Kaufmann H, Elliovich F: An unusual cause of tetany: surreptitious use of furosemide, 51(5):625–628.
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Khilnani MT: *see* Keller RJ.
Kirban EH: *see* Zinn KM.
Korelitz BI: The ileorectal and ileosigmoidal fistula in

Crohn's disease: a clinical-radiological correlation, 51(4):341–346.
Krasna I: Infant: right to privacy and patient's right to know, 51(1):25–28; *see* Discussion, Beginning of life.
Kravitz L: Rabbinic comment: Infant with severe anomalies: should life-saving surgery be performed? 51(1):34–41; *see* Discussion, Beginning of life.
Kreel I: *see* Salky B.
Kurzban JD: *see* Maklansky D.

Laboratory testing on admission to a teaching service: expectations and outcomes for serum electrolytes, Murata GH, Muranaka E, Ellrodt AG, 51(2):141–147.
Late Dacron graft failure: two cases, Ahwah I 51(6):728–731.
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Lee RE: *see* Ornellas EP.
Leishmeniasis, Levitan H, Kantor I, Levitan LJ, Levitan M, 51(3):274–282.
Letter to the editor: the graffiti pharmacopeia, Marks SJ, 51(5):647.
Levitan H, Kantor I, Levitan LJ, Levitan M: Leishmaniasis, 51(3):274–282.
Levitan LJ: *see* Levitan H.
Levitan M: *see* Levitan H.
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Lichtenstein JE: *see* Olmstead WW.
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Lindner AE: *see* Maklansky D.
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Lu CH, Franken EA: Snail-like spiral deformity of the stomach (Schneckenförmige Einrollung), 51(4):404–407.
Lubin J, Mark TM, Wirtschafter AR: Papillomas of prostatic urethra with prostatic-type epithelium: report of eight cases, 51(2):218–221.

McClees EC: *see* Gedgaudas-McClees RK.
McCort JJ: Anterior pararenal-space infection from colon and appendiceal perforation, 51(4):482–490.
McCort JJ: *see* Singleton EB.
McMichan JC: Continuous monitoring of mixed oxygen saturation in clinical practice, 51(5):569–572.
Magana L, Dhar SK, Smith EC, Martinez C: Iron absorption and utilization in maintenance hemodialysis patients: oral and intravenous routes, 51(2):180–183.
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Maklansky D, Lindner AE, Kurzban JD: Richard H. Marshak, M.D. An appreciation, 51(4):313–317.
Maklansky D, Rabinowitz J, guest ed: Gastrointestinal radiology: a festschrift for Richard H. Marshak, M.D., 51(4)311–558.
Marks SJ: Letter to the editor: the graffiti pharmacopeia, 51(5):647.
Mark TM: *see* Lubin J.
Marshak, Richard H Festschrift: 51(4):311–558; An appreciation, Maklansky D, Lindner AE, Kursban JD, 51(4):313–317.
Martinelli GP: *see* Racelis D.
Martinez C: *see* Magana L.
Martinez LA, Francis DA, Schilling KJ, Cohen BM: Diagnosis of polar hypertrophy of kidney: case reports and review, 51(6):697.
Maxwell MH: *see* Waks AU.
Medical ethics: the Jewish point of view, Gribetz D, Tendler MD, guest eds., 51(1):1–120.
Meschan I: Overview and summary of roentgen signs of diseases of the small bowel, 51(4):319–336.
Miller R: *see* Plosker H.
Mindich BP: *see* Reder RF.
Mlsna J, Rubenstone AI, Reyes MG, Thomas W Jr, Reproducibility of the red-cell-adherence test: technical and practical considerations, 51(2):203–206.
Moon RC: *see* Ornellas EP.
Morgenthau JE: Teenage pregnancies and abortion, 51(1):18–19.
Moshirpur J: *see* Abramson A.
Moskowitz N: Evoked potentials in diagnosis, prognosis, and management of neurologic and neurosurgical patients, 51(5):640–643.
Mount Sinai Hospital Medical Center of Chicago; affiliates with *Journal,* 51(1):v; history and introduction, 51(2):149; articles from, 51(2):149–207; editorial, 51(6):649.
Mount Sinai Medical Center of Greater Miami: affiliates with *Journal,* 51(1):v; history and introduction, 51(2):209; articles from, 51(2):209–226; editorial, 51(6):649.
Muranaka E: *see* Murata GH.
Murata GH, Muranaka E, Ellrodt AG: Laboratory testing on admission to a teaching service: expectations and outcomes for serum electrolytes, 51(2):141–147.

Nardi L, Constantini S: An association of parotid carcinoma with Von Hippel-Landau syndrome, 51(3):298–299.

O'Brien A: *see* Ornellas EP.
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Oral barium tracer: an adjunct for enema preparation, Pochaczevsky R. 51(4):479–481.
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Oshins J: *see* Weinstein RS.

Overview and summary of roentgen signs of diseases of the small intestine, Meschan I, 51(4):319–336.
Ovsyshcher IA: *see* Zimlichman R.

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Papago Indians: historical, social, and medical perspectives, Hoffman BH, Haskell AJ, 51(6):707.
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Pathophysiologic approach to nontumorous small-bowel disease, Olmstead WW, Lichtenstein JE, 51(4):360–367.
Percutaneous drainage of abdominal abscesses and fluid collections, Ferrucci JT Jr, 51(4):547–551.
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Perec CJ: *see* de Peusner ICW; Tiscornia OM.
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Pochaczevsky R: Oral barium tracer: an adjunct for enema preparation, 51(4):479–481.
Post-ischemic bowel obstruction in the low-birth-weight infant, Singleton EB, 51(4):465–466.
Postsurgical adult respiratory distress syndrome: case report, Epstein M, Stern AJ, 51(3):305–310.
Practice of tubal sterilization: review of a departmental practice pattern, Gleicher N, Deppe G, Friberg J, 51(2):157–160.
Propranolol-induced myotonia, Turkewitz LJ, Sahgal V, Spiro A, 51(2):207.
Prospects in medical care: physicians, patients, practice, Ginzberg E, 51(3):258–261.
Pulmonary artery catheterization: past, present, and future, Thys DM, 51(5):578–584.
Purulent pericarditis caused by streptococcus anginosus-constellatus, Reder RF, Raucher H, Cesa M, Mindich BP, 51(3):295–297.
Puszkin S: *see* Lewis W.

Rabinowitz JG: Introduction (Gastrointestinal radiology: a festschrift for Richard H. Marshak, M.D.), 51(4):311; Radiology Notes (editor), 51(5):633.
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Racelis D, Martinelli GP, Schanzer H: Effects of antithymocyte serum on cardiac allograft survival in thymectomized-splenectomized rats, 51(3):262–267.
Radiologic evaluation of the portal system by the newer modalities of computed tomography and ultrasound, Ruzicka FF, 51(4):516–527.
Radiology notes: Case 1, Ruchman RB, Keller RJ, Sicular A, Hauser AD, 51(5):633–636; Case 2, Gendal ES, Keller RJ, Sicular A, Waye JD, Cornell A, 51(5):637–639.
Ralph Colp Award, 51(5):601.
Raucher H: *see* Reder RF.
Reder RF, Raucher H, Cesa M, Mindich BP: Purulent pericarditis caused by streptococcus anginosus-constellatus, 51(3):295–297.
Relationship of hyperactivity of the duodenal autonomic nervous brain (duodeno-pancreatic reflexes) and enhanced "pancreon" secretory response to CCK-PZ in chronic alcoholism, Tiscornia OM, Perec CJ, Celener D, Cresta MA, Tumilasci OR, de Lehmann ES, Dreiling DA, 51(6):650.
Renal dysplasia and chondrodysplasia in the ch hydrocephalic mouse: a cellular model of defective differentiation and organization, Richardson RR, Reyes MG, 51(2):188–196.
Reproducibility of the red-cell-adherence test: technical and practical considerations, Mlsna J, Rubenstone AI, Reyes MG, Thomas W Jr, Noronha R, 51(2):203–206.
Response of plasma norepinephrine levels to stimulation in renovascular hypertension, Waks AU, Burkhalter JF, Maxwell MH, 51(6):687.
Reyes MG, Yastrow ES: Stereologic analysis of muscle capillaries in selective atrophy of type 2 myofibers, 51(2):184–187.
Reyes MG: *see* Mlsna J; Richardson RR.
Richardson RR, Reyes MG: Renal dysplasia and chondrodysplasia in the ch hydrocephalic mouse: cellular model of defective differentiation and organization, 51(2):188–196.
Rico M: Breast cancer: risk factors and etiology, 51(3):300–304.
Rights of adolescents in a medical setting, Young JG, 51(1):42–48; Rabbinic comment, Feldman DM, 51(1):49–51.
Rimarenko S, Jagirdar J: Veno-occlusive syndrome of the liver in an alcoholic man, 51(3):292–294.
Risk-benefit ratio: hazardous surgery and experimental therapy, Rosner F, 51(1):58–59; Rabbinic comment, Tendler MD, 51(1):60–64.
Role of pharmacotherapy in secondary prevention of myocardial infarction and death, Gorlin R, Fuster V, 51(3):229–236.
Rosner F: Risk-benefit ratio: hazardous surgery and experimental therapy, 51(1):58–59; *see* Discussion, Adolescence to adulthood.
Rovinsky JJ: Abortion on demand, 51(1):12–14; *see* Discussion, Beginning of life.
Rubenstein AE: see Neurology Notes (editor), 51(5):625.
Rubenstone AI: *see* Mlsna J.
Rubin KP: *see* Field SP.
Ruchman RB, Keller RJ, Sicular A, Hauser AD: Radiology notes: Case 1, 51(5):633–636.

Ruzicka FF: Radiologic evaluation of the portal system by the new modalities of computed tomography and ultrasound, 51(4):516–527.
Ryo UY: *see* Chang JL.

Sachar DB: *see* Field SP; Gastroenterology Notes (editor), 51(5):620.
Sackner MA: Effects of hydrocone bitartrate on breathing pattern of patients with chronic obstructive pulmonary disease and restrictive lung disease, 51(2):222–226.
Sacks HS: *see* Weinstein RS.
Sahgal V: *see* Turkewitz LJ.
Salky B, Katsoyannis G, Aufses AH, Kreel I: Splenectomy for chronic idiopathic thrombocytopenic purpura, 51(3):287–289.
Salomonowitz E: *see* Frick MP.
Savitz MH, Katz SS: Use of the one-piece shunting system in adults, 51(3):271–273.
Schanzer H: *see* Racelis D.
Schilling KJ: *see* Martinez LA.
Schwab RE, Bree RL: Ultrasound and computed tomography in the evaluation of inflammatory bowel disease, 51(4):398–399.
Schwartz MG, Sgaglione NA: Gastric CA, 51(6):720.
Seaman WB: Abnormal mucosal fold patterns in the duodenum, 51(4):421–428.
Sheldon SH: *see* Levy HB.
Shewchun J: *see* Ho CS.
Sicular A: *see* Gendal ES; Ruchman RB.
Siegel JH: Interventional endoscopy in diseases of the biliary tree and pancreas, 51(4):535–542.
Silvay G, guest ed: Twenty-first Bernard H. Eliasberg Memorial Symposium. Recent advances in monitoring during anesthesia, 51(5):559–647; Introduction: Twenty-first Eliasberg memorial symposium: recent advances in monitoring during anesthesia, 51(5):559.
Silvay G, Griffin BM: History and development of cardiovascular monitoring during anesthesia, 51(5): 560–568.
Silver C: *see* Wolfe RD.
Single-contrast and double-contrast radiography in the detection of gastritis, Thoeni RF, 51(4):408–416.
Single-contrast or double-contrast barium enema: a historical and philosophical perspective, Dreyfuss JR, Janower ML, 51(4):461–464.
Singleton EB: Post-ischemic bowel obstruction in the low-birth-weight infant, 51(4):465–466.
Singleton EB, McCort JJ: Comments, Gastrointestinal radiology: a festschrift for Richard H. Marshak, M.D., 51(4):312.
Small-bowel changes secondary to Intraperitoneal leakage from dermoid cyst of the ovary, Wolfe RD, Weinreb I, Silver C, 51(4):382–386.
Smith EC: *see* Magana L.
Smith HJ, Willeford G, Aueron FM: Esophagus and stomach after proximal gastric vagotomy, 51(4):417–420.
Smith JL Jr: *see* Keen SJ.
Snail-like spiral deformity of the stomach (Schneckenförmige Einrollung), Lu CH, Olson J, Franken EA, 51(4):404–407.
Sparks JC: *see* Aubry WM.
Sperling R: *see* Abramson A.
Spiera H: Dose-related nephrotic syndrome in pencillamine-treated rheumatoid arthritis, 51(6):695.
Spiro A: *see* Turkewitz LJ.
Splenectomy for chronic idiopathic thrombocytopenic purpura, Salky B, Katsoyannis G, Aufses AH, Kreel I, 51(3):287–289.
Splenic cystectomy and splenic preservation, Hodgson WJB, 51(4):543–546.
Staging of lymphoma and testicular carcinoma, Torres WE, Bernardino ME, 51(4):502–507.
Stereologic analysis of muscle capillaries in selective atrophy of type 2 myofibers, Reyes MG, Yastrow ES, 51(2):184–187.
Stern AJ: *see* Epstein M.
Steroid-responsive dysphagia: a clue to the diagnosis of esophageal lymphoma, Field SP, Sachar DB, Childs CC, Rubin KP, 51(4):451–454.
Student prize 1983/1984, Rico M, 51(5):601.
Surgical management of duodenal duplication cyst simulating pyloric stenosis, Pober JM, Bleicher MA, 51(6):702.
Synovial sarcoma of anterior abdominal wall, Faerber EN, Leonidas JC, Bhan I, 51(6):705–706.
Szabo D: *see* Papp M.

Taylor M: *see* Harell GS.
Teele RL: A dozen pediatric ultrasonic donuts, 51(4):528–534.
Teenage pregnancies and abortion, Morgenthau JE, 51(1):18–19; Rabbinic comment, Feldman DM, 51(1):20–24.
Tendler MD: Rabbinic comment: In vitro fertilization ("test-tube" baby), 51(1):7–11; The infant: right to privacy and patient's right to know, 51(1):29–31; Risk-benefit ratio: hazardous surgery and experimental therapy, 51(1):60–64; Transplantation surgery, 51(1):54–57; *see* Discussion, Adolescence to adulthood; Beginning of Life; End of life; Triage of scarce resources.
Tendler MD, Gribetz D, guest eds, Medical ethics: the Jewish point of view 51(1):1–120; Introduction, 51(1):1–2.
Teramura K: *see* Reyes MG.
The Mount Sinai Journal: awards 1983/84, 51(5):601; Editorial, 51(6):649. Future, Dreiling DA, 51(1):v; Past, Tuchman LR, 51(1):i–iv.
The Mount Sinai Journal: Past, Tuchman LR, 51(1): i–iv.
Thoeni RF, Single-contrast and double-contrast radiography in the detection of gastritis, 51(4):408–416.
Thomas W Jr, Zaret P: Cholesterol emboli causing acute gangrenous cholecystitis, 51(6):716.
Thomas W Jr: Pathology Notes (ed), 51(6):716; *see* Mlsna J; Ornellas EP.
Thys DM: Pulmonary artery catheterization: past, present, and future, 51(5):578–584.
Tiscornia OM, Perec CJ, Celener D, Cresta MA, Tumilasci OR, de Lehmann ES, Dreiling DA: Relationship of hyperactivity of the duodenal autonomic nervous brain (duodeno-pancreatic reflexes) and enhanced "pancreon" secretory response to CCK-PZ in chronic alcoholism, 51(6):650.
Tiscornia OM: *see* de Peusner ICW; Perec CJ.
Tishler JMA: Tuberculosis of the small intestine, 51(4):337–340.

Torres WE, Bernardino ME: Staging of lymphoma and testicular carcinoma, 51(4):502–507.
Transplantation surgery, Griefer I, 51(1):52–53; Rabbinic comment, Tendler MD, 51(1):54–57.
Trainin I: *see* Discussion, Medical ethics, End of life.
Transesophageal echocardiography, Kaplan JA, 51(5):592–594.
Treatment of gastrinoma, Zollinger RM, 51(4):401–403.
Triage of resources from departments to patients, Griefer I, 51(1):110–112; Rabbinic comment, Gellman MA, 51(1):113–115.
Triage of resources from government to institutions, Chalmers TC, 51(1):101–103.
Triage of resources from institutions to departments, Begun MS, 51(1):104–105; Rabbinic comment, Tendler MD, 51(1)106–109.
Trophic, biochemical, and functional changes in submaxillary glands and pancreas induced by chronic alcohol feeding mediated by parasympathetic autonomic centers, Perec CJ, Tiscornia OM, Baratti MD, Tumilasci OR, Dreiling DA, 51(6):664.
Tuberculosis infection in Mount Sinai medical students, Weinstein RS, Oshins J, Sacks HS, 51(3):283–286.
Tuberculosis of the small intestine, Tishler, JMA, 51(4):337–340.
Tuchman LR: The Mount Sinai Journal: Past, 51(1): i–iv.
Tumilasci OR: *see* Perec CJ.
Tumilasci OM: *see* Tuscornia OM.
Turkewitz LJ, Sahgal, V, Spiro A: Propranolol-induced myotonia, 51(2):207.
Twenty-first Eliasberg memorial symposium: recent advances in monitoring during anesthesia, Introduction, Silvay G, ed., 51(5):559.
Tymorek S: *see* Westerman MP.

Ultrasound and computed tomography in the evaluation of inflammatory bowel disease, Schwab RE, Bree RL, 51(4):387–399.
Ultrastructural study of faces of diseases, Reyes MG, Termura K, 51(6):714.
Use of the one-piece shunting system in adults, Savitz MH, Katz SS, 51(3):271–273.

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Varro V: *see* Pap A.
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Waye JD: Diagnostic approach to colon bleeding, 51(4):491–500; *see* Gendal ES.
Weinreb I: *see* Wolfe RD.
Weinstein RS, Oshins J, Sacks HS: Tuberculosis infection in Mount Sinai medical students, 51(3):283–286.
Westerman MP, Tymorek S: A history of medical research at Mount Sinai Hospital Medical Center of Chicago, 51(2):150–156.
Westerman MP: *see* Ornellas EP; Venkataraman M.
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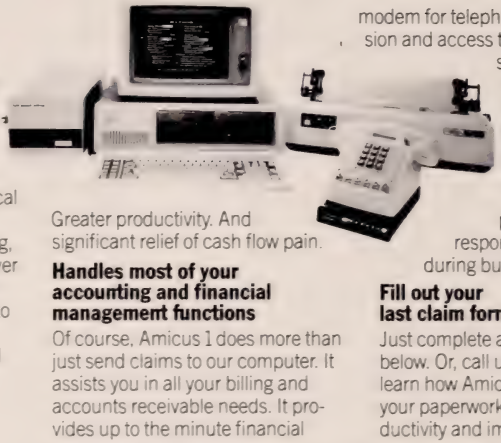

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